Vincent Cottin
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Luca Richeldi
Editors

Orphan Lung Diseases

A Clinical Guide to Rare Lung Disease

Springer

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

Vincent Cottin

Preface

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 6,000–8,000 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 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 sections, 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.

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Contents

Section I Introduction

1 Orphan Lung Diseases from Definition to Organisation of Care 1
Jean-François Cordier and Vincent Cottin

2 The Challenges of Clinical Research in Orphan Diseases 5
Paolo Spagnolo and Roland M. du Bois

Section II Orphan Diseases of the Airways

3 Chronic Bronchiolitis in Adults 17
Talmadge E. King Jr.

4 "Diffuse Bronchiectasis of Genetic Origin" 29
Jane S. Lucas and Katharine C. Pike

5 Allergic Bronchopulmonary Mycosis 53
Isabelle Tillie-Leblond†, Jean-François Bervar, and Antoine Deschildre

6 Orphan Tracheopathies 73
Fabien Maldonado, Sara Tomassetti, and Jay H. Ryu

Section III Systemic Disorders with Lung Involvement

7 Amyloidosis and the Respiratory Tract 91
Christopher P. Venner, Jennifer H. Pinney, and Helen J. Lachmann

8 Eosinophilic Granulomatosis with Polyangiitis (Churg–Strauss Syndrome): A Clinical and Therapeutic Approach 113
Loïc Guillevin and Matthieu Groh

9 Granulomatosis with Polyangiitis (Wegener's Granulomatosis) 127
Christian Pagnoux and Alexandra Villa-Forte

10 Alveolar Hemorrhage 155
Jason Wells and Stephen K. Frankel

11 Pulmonary Involvement in Takayasu Arteritis and Behçet Disease 177
Laurent Arnaud, Miguel Hie, and Zahir Amoura

12 Pulmonary Vascular Manifestations of Hereditary Hemorrhagic Telangiectasia 191
Els M. de Gussem and Marie E. Faughnan

13 Hepatopulmonary Syndrome 201
Karen L. Swanson

14 Non-Langerhans Cell Histiocytosis-Including Erdheim-Chester Disease- and the Lung 211
Julien Haroche, Anne-Laure Brun, Frédérique Capron, Frédéric Charlotte, Philippe A. Grenier, and Zahir Amoura

Section IV Lung-dominant or -Limited Orphan Diseases

15 Eosinophilic Pneumonia 227
Vincent Cottin and Jean-François Cordier

16 Multiple Cystic Lung Diseases 253
Jean-François Cordier, Vincent Cottin, Chahéra Khouatra, Sophie Giraud, and Romain Lazor

17 Lymphangioleiomyomatosis 271
Simon R. Johnson

18 Pulmonary Alveolar Proteinosis 285
Raphael Borie, Pauline Pradère, Claire Danel, Marie-Pierre Debray, and Bruno Crestani

19 Exogenous Lipoid Pneumonia 295
Anne Gondouin and Jean-Charles Dalphin

20 Pulmonary Alveolar Microlithiasis 305
Salvatore Mariotta, Alessandro Onofri, Pierdonato Bruno, and Alberto Ricci

Section V Orphan Interstitial Lung Diseases

21 Pulmonary Fibrosis and the Many Faces of UIP 315
Stefania Cerri, Giacomo Sgalla, Giulio Rossi, Giovanni Della Casa, and Luca Richeldi

22 The Syndrome of Combined Pulmonary Fibrosis and Emphysema 327
Vincent Cottin and Jean-François Cordier

23 Non-specific, Unclassifiable, and Rare Idiopathic Interstitial Pneumonia: Acute Interstitial Pneumonia, Respiratory Bronchiolitis Interstitial Pneumonia, Desquamative Interstitial Pneumonia, Nonspecific Interstitial Pneumonia 349
Curtis J. Coley II, Leslie B. Tolle, Jennifer Hasvold, Lindsay A. Schmidt, and Kevin R. Flaherty

24 Organizing Pneumonias 363
Romain Lazor

25 Interstitial Lung Disease in Systemic Sclerosis 379
Athol U. Wells, George A. Margaritopoulos, Katerina M. Antoniou, and Andrew G. Nicholson

26 Interstitial Lung Disease in Connective Tissue Diseases Other Than Systemic Sclerosis 391
Bruno Crestani, Marie-Pierre Debray, Claire Danel, Mathilde Neuville, Raphael Borie, Camille Taillé, Laurent Plantier, and Michel Aubier

27 Interstitial Lung Disease in Undifferentiated Forms of Connective Tissue Disease 419
Aryeh Fischer and Kevin K. Brown

28 Pulmonary Langerhans Cell Histiocytosis and Smoking-Related Interstitial Lung Diseases 435
Carlo Vancheri and Silvia Puglisi

29 Rare Causes and the Spectrum of Hypersensitivity Pneumonitis 457
Jean-Charles Dalphin and Anne Gondouin

30 Chronic Beryllium Disease and Other Interstitial Lung Diseases of Occupational Origin 473
Joachim Müller-Quernheim, Gernot Zissel, Gian Kayser, and Antje Prasse

Section VI Miscellaneous Orphan Lung Diseases

31 Lymphoproliferative Lung Disorders 493
Venerino Poletti, Gian Luca Casoni, Sara Piciucchi, Sara Tomassetti, Silvia Asioli, Alessandra Dubini, and Marco Chilosi

32 Pulmonary Manifestations of Hematological Malignancies: Focus on Pulmonary Chronic Graft-Versus Host Disease 517
Karine Chagnon, Frédéric Schlemmer, Véronique Meignin, and Anne Bergeron

33 Pulmonary Hypertension in Orphan Lung Diseases 529
David Montani, Barbara Girerd, Andrei Seferian, Laurent Godinas, and Marc Humbert

34 Rare and Emergent Drug-Induced and Iatrogenic Respiratory Conditions: A Guide to Their Recognition and Management 541
Philippe Bonniaud and Philippe Camus

35 From Cancer Mimicking Orphan Lung Disease to Orphan Thoracic Oncology 581
Nicolas Girard, Vincent Cottin, and Jean-François Cordier

36 Rare Diffuse Lung Diseases of Genetic Origin 597
Paolo Spagnolo

Index 611

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Orphan Lung Diseases from Definition to Organisation of Care

1

Jean-François Cordier and Vincent Cottin

Definitions

The rare diseases have been called "orphan" because this term means that patients affected by such conditions feel that most physicians are reluctant to care for their disease because of its rarity, and that insufficient research is developed to improve diagnosis, clinical management, and especially the more distressing manifestations. The patients with rare diseases thus feel abandoned and orphan when comparing with patients with common diseases who benefit from extensive research worldwide and continuous drug development.

It is worthwhile mentioning that not all orphan diseases are rare: some may be common but neglected because they affect people in poor countries (e.g. chronic infectious tropical diseases).

The definition of rare disease in Europe is a prevalence of less than 1:2,000, and fewer than 200,000 people in the USA. However there is currently no established definition for the so-called "ultra-rare" diseases which affect even much smaller populations, with a prevalence as low as 1:2,000,000, or even less [1]. Somewhat rare and ultra-rare lung diseases delineate a spectrum of rarity resulting in specific differences (e.g. recruitment for clinical trials often insufficient for solid methodology) [2, 3].

The Wide Spectrum of Rare Pulmonary Diseases

The number of *all* rare diseases and syndromes has not been hitherto established however these have been estimated between 6,000 and 8,000, with a large proportion being of genetic origin. However most rare *lung* diseases are idiopathic and chronic rather than of genetic origin.

Rare diseases limited to the lung may be acquired (*e.g. hypersensitivity pneumonitis*) or be of genetic origin (e.g. *diffuse interstitial lung disease in children with surfactant proteins gene mutations*).

Pulmonary involvement may occur in acquired rare systemic disorders (e.g. *granulomatous polyangiitis*) or in disorders of genetic origin (e.g. *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*). Overlap 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 in the present book has progressively emerged from a variety of disorders which themselves may represent diagnostic challenges when almost similar clinical and/or imaging features are present especially the rare pulmonary tumours (e.g. *primary pulmonary lymphoma*) or rare infections (e.g. *atypical mycobacterial infections*). The differential diagnosis of any rare pulmonary disease should thus always take into consideration the possibility of neoplastic or infectious disorders.

Diagnostic Challenges

The diagnostic delays are the major complaint of patients, with a definite diagnosis obtained only after several years in a large proportion of cases.

It is evident that the general practitioner cannot be aware of the thousands of rare diseases with their phenotypes and diverse presentations. However medical education should better develop the need of systematic consideration of a possible rare disease for any patient with atypical features of a suspected common disease, and teach the further necessity

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of checking (especially on Orphanet) which possible rare diseases may fit with the observed atypical clinical presentation.

Such patients should be systematically referred to a respiratory specialist for either confirming an atypical presentation of a common disease, or validating the hypothesis of a rare pulmonary disease. Because of the complexity of most rare pulmonary diseases, we consider that any patient with rare disease should benefit from a medical advice or evaluation at an expert centre, for confirmation (or making) of a precise and definite diagnosis further resulting in specialised standard of care. Such patients must be advised to contact patient organisations and to meet especially expert patients. They should further be informed about possible participation in studies and clinical trials.

Expert Centres

Although there are no established criteria of expertise there is informal agreement that national expert centres should be referral structures for a given rare disease (or group of rare diseases) associating clinical experience (based on a large recruitment of patients for diagnosis and management) together with active clinical research (validated by international scientific publications) and with further cooperation with research laboratories in the field.

The first role of expert centres is to appropriately diagnose or confirm the diagnosis of a rare disease, and to propose up to date treatment and management.

The designation of expert centres in France has validated 132 national *reference centres* (including one adult pulmonary centre in Lyon and one pediatric pulmonary centre in Paris) with further regional *competence centres* in respiratory departments of most university hospitals. The role of the reference centres especially comprises the production of diagnostic and management procedures, the evaluation of referred individual complex cases, the development of registries, the design and coordination of clinical research on the diseases and their treatment, and epidemiology studies. The competence centres together with their reference centre form a tight network allowing equity in the access to care for all patients over the country, and further they actively contribute to clinical research.

The European Union Committee of Experts on Rare Diseases (EUCERD) entrusted with aiding the European Commission laid down foundation for the rare disease community regarding the centres of expertise, European Reference Networks, patients registries and data bases, newborn screening, and indicators for national rare diseases plans/strategies [4, 5].

Patient Organisations

National patients organisations and advocacy groups have developed for most rare diseases throughout the world [6, 7]. These most often resulted from the efforts of obstinate pioneer 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 rising of funds, the organisation of annual meetings where patients (and their family) and doctors from expert centres meet, and national and international cooperation of patients have dramatically increased in the last decades [8].

Further alliances of patients' organisations have developed at the international level especially in the USA (National Organisation for Rare Disorders, NORD) and in Europe (European Organisation for Rare Diseases, EURORDIS).

Clinical Trials

The clinical trials of drugs and procedures in patients with rare diseases are first faced with the recruitment of adequate numbers of patients. In addition to the rarity of patients, a major challenge is the recruitment of patients with relatively early disease thus accessible to improvement (or at least stabilisation) 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).

The standard randomised, double-blind, placebo-controlled trials for the evaluation of new drugs in very rare disease are often prevented by difficulties in the recruitment of patients, thus leading to use alternative suboptimal study designs and methods, and clinically meaningful endpoints.

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 [7]. The "orphan" status allows sponsors to benefit from incentives for the development of drugs (and further medical devices or drug products).

In Europe the regulation on orphan medical products was adopted in 1999. Marketing exclusivity for orphan drugs is for 7 years in the US and 10 years in the EU.

Empowerment of Patients

The empowerment of patients is a necessity especially for patients with rare diseases because these are chronic, difficult to manage, and necessitate coordinated efforts to make progress [6, 8].

The ideal expert-patient with rare disease should have both personal and collective experiential knowledge of illness as well as academic involvement including knowledge of the disease and its treatment, academic formation as educator/teacher with health professionals in patient education (including self-management), willingness to take into account patient values and priorities for decision making, collaborative relationship with academic specialists, responsibilities in patients' associations (e.g. as board member), attendance and active participation in regional/national/international patient meetings, and participation as partner in the design of clinical studies/therapeutic trials [9].

Orphanet

Orphanet (www.orpha.net) is a portal for rare diseases and orphan drugs providing comprehensive information about the classification of rare diseases, an encyclopedia of rare diseases including assistance to diagnosis tools, emergency guidelines, inventory of orphan drugs, directory of expert centres and patient organisations, directory of professionals and institutions, etc.

Research in Orphan Lung Diseases

The future of patients with orphan lung diseases relies on both the access of all patients to definite diagnosis and optimal current care, and further on both clinical and basic research.

Research started with early observation of curious single cases initially based on dysmorphy. Over time morphologic and pathologic features of single cases or short series of patients identified specific syndromes or diseases. Advances in morphologic studies were followed by basic research with exponential capacities in extended gene analysis. The identification of biopathological mechanisms of disease supported by public and private institutions, and further by patients [9] have opened the way for individual comprehensive care from symptoms to efficient treatment.

Box 1.1

Methodical Doubt for Rare Disease

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

Some examples:

- idiopathic bilateral lower lobes bronchiectasis in a 34 year-old man with further chronic rhinitis and sinusitis (*could it be primary ciliary dyskinesia* ?)
- rapidly progressive dyspnea with diffuse infiltrative lung disease on chest X-ray with severe increasing anaemia (*could it be alveolar haemorrhage* ?)
- pneumothorax in a patient with polydyspsia (*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* ?)

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The Challenges of Clinical Research in Orphan Diseases

2

Paolo Spagnolo and Roland M. du Bois

You only find what you look for and you only look for what you know

Abbreviations

BHD	Birt-Hogg-Dubé
COPD	Chronic obstructive pulmonary disease
EURORDIS	European Organization for Rare Diseases
FDA	Food and Drug Administration
FLCN	Folliculin
GM-CSF	Granulocyte macrophage-colony stimulating factor
IPF	Idiopathic pulmonary fibrosis
LAM	Lymphangioleiomyomatosis
MTOR	Mammalian target of rapamycin
PAP	Pulmonary alveolar proteinosis
SP	Surfactant protein

Introduction

Rare diseases represent a significant burden on global society. There are roughly 8,000 rare diseases that are, in Europe, defined as diseases that affect less than 1:2,000 individuals. In the US, the Rare Disease Act of 2002 and the US Orphan Drug Act defines 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 and 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" (orphan disease). In this context, rare lung diseases represent a group of disorders linked by the common qualities of being infrequent and unusual. As with all rare diseases, these conditions are generally poorly studied – thus incompletely understood – and often have no effective therapy; individuals who have the misfortune to be suffering from a rare, poorly understood disorder feel marginalized and orphaned, hence the commonly applied term "orphan" disease. About 10 % of all diseases are classified as rare, and their cumulative prevalence is about 6–8 %, representing an important public health concern [1] Despite an urgent need, boosting research in rare diseases can be particularly frustrating for a number of reasons (Table 2.1):

1. Many diseases lack any "research community".
2. Scientists are often scattered within a country or even internationally, which makes unfeasible gathering different expertise in a multidisciplinary approach.
3. Resources needed to conduct research may be similarly scattered or altogether lacking, e.g., databases, biological resource centers and registries.
4. Research into rare diseases may be more costly and time-consuming than in other areas as researchers may need to build *ex novo* their links with scientists in other disciplines, gather scarce data and deal with uncertain funding.

Table 2.1 Common challenges in rare lung diseases

Increasing awareness of rare diseases throughout society
Defining disease mechanisms and targets – encourage basic research
Improving case definition
Improving methods of diagnosis and screening
Standardizing methods for sample manipulation and analysis
Building up dedicated registries
National and international research networking
Continuous interactive feedback between disciplines
Integrating clinical research and patient care
Recruiting participants to clinical trials
Raising funding
Optimizing academia-industry interaction
Translating new data into the clinic and health decision making
Orphan diseases in developing countries

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5. Scientists are often more interested in mechanisms than how mechanistic interventions might improve disease management so fail to collaborate with clinician-scientists to identify approaches to treatment.
6. Due to the lack of commercial interest related to research in rare diseases, clinician-scientists may be reluctant to pursue a career in these arenas

Several fundamental factors impose obstacles that prevent scientists and clinicians collaborating on research into orphan diseases and these challenges need to be overcome to allow a significant percentage of the global community to feel that they are not forgotten.

Challenges to Be Overcome in Order to Undertake Quality Clinical Research

In order to undertake clinical research there need to be adequate numbers of patients gathered, either in a single centre or through clinical networks, to enable meaningful data to be obtained but this task is problematic for a number of reasons that include: the general paucity of prevalence and incidence data, despite the existence of registries; small numbers of patients with any individual disease; the variable genetic effects with incomplete penetrance that affect disease expression; the genetic factors that impact specific phenotypes; the occurrence of some genetic diseases in only certain populations worldwide; and gene-environment interactions. Compounding these problems are the considerable challenges that patients have to overcome in their efforts to obtain a speedy and accurate diagnosis of their rare illness; they, therefore, often present late in their disease when it is 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 affected from region to region and country to country. The prevalence of rare lung diseases varies widely by disease type and is difficult to estimate for a number of reasons. A "common" rare disease, such as sarcoidosis, can occur in up to 70 patients per 100,000 in some countries, although it is much less prevalent in other countries [2, 3]; conversely, other disorders (including, for example, pulmonary alveolar microlithiasis, surfactant protein [SP]-A-related lung disease, idiopathic pulmonary haemosiderosis) have only been described in case reports or small case series. The lung may also be involved as a rare manifestation of more common disorders, such as Marfan's syndrome, Ehlers-Danlos syndrome, Gaucher's disease or Neiman Pick type C disease. In rare diseases, there is much less evidence base on which to make treatment decisions than in more common lung diseases such as asthma or chronic obstructive pulmonary disease (COPD).

Small Numbers

Investigators interested in performing clinical studies of rare diseases or trials of orphan drugs are faced with challenges usually not encountered in clinical trials of larger populations. Obvious drawbacks include the small size of the trial population and the fact that patients are often geographically dispersed, thus with an inherent diversity of healthcare system. This is particularly true for disorders with geographic prevalence (Hermansky-Pudlak syndrome in Puerto Ricans) or gender predominance (lymphangioleiomyomatosis [LAM] in women of childbearing age). In these circumstances, it is almost impossible to undertake the randomized, double/blind, placebo-controlled studies that now represent the *gold standard* of clinical trials, on which quality of evidence judgements are made. In this regard, the choice of appropriate trial methodology and meaningful outcome parameters is a matter of intense debate in even those disease such as idiopathic pulmonary fibrosis (IPF) where there are robust end point data and the disease is sufficiently common for large clinical trials of therapy to have been undertaken. In rarer diseases, in order to prove efficacy in a study with small patient numbers, the compound under investigation needs to show a stronger treatment effect than in a study with large numbers, thus highlighting the need for more robust methods of data analysis for small samples. Likewise, drawing conclusions from trials performed in a limited number of patients may be dangerous. Good examples include several early studies investigating antiestrogen therapy – consisting of surgical castration by oophorectomy, administration of tamoxifen, progesterone, and gonadotropin-releasing hormone agonist or luteinizing hormone-releasing hormone – that have reported beneficial effects in LAM [4, 5]. Subsequent careful scrutiny of some of these studies has, however, revealed that while the treatment under investigation may have improved some aspects of the disease, for example chylothorax or chylous ascites, other affected organs including especially pulmonary involvement, were not affected and in some instances progression was the outcome. Now that lung transplantation has become an acceptable treatment option for patients with LAM, more experimental treatments must be used with caution because of the potential complications due to adverse effects that might jeopardise the eligibility for or outcome after lung transplantation. A good example is the use of surgical or medical castration that may not produce any beneficial effect on the disease course, but may exert long-term effects on bone metabolism, particularly in the postoperative period of lung transplantation.

Genetic Component with Variable Degree of Penetrance

It is estimated that 80 % of the identified rare diseases have a genetic origin. However, the importance of environment triggers, in addition to the genetic susceptibility, is becoming increasingly clear. Many diseases require this gene/environment interaction to manifest. Furthermore, different combinations of genetic susceptibility and individual trigger agents are also likely to explain diversity in terms of organ manifestations and disease severity, which, in turn, accounts for the inconsistent genotype-phenotype correlations. A good example includes chronic beryllium disease where a powerful genetic predisposition requires less antigenic stimulus but stronger environmental exposures can provoke disease in those individuals who have less strong susceptibility genotypes [6].

Rare 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(3). Available measures of prevalence suggest that it is not a common disease. United Kingdom mass surveys in the 1950s and 1960s disclosed radiographic abnormalities consistent with sarcoidosis in 9 [7] to 36 [8] per 100,000 of those screened. Similar studies in Scandinavia, carried out over the same decades, revealed a combined prevalence of 28 per 100,000 examined persons [9]. In 1964, Bauer and Löfgren [10] summarized the findings from 29 surveys (in ten cases nationwide) carried out in 24 countries; the results varied widely from 0.2 per 100,000 (in Portugal, Brazil, and Uruguay) to the highest figure of 64 per 100,000 in Sweden. In general the prevalence is higher the greater the degrees of latitude from the equator for reasons that are not understood. In the USA, sarcoidosis is more common in African Americans than whites. Applying cumulative incidence estimates, the lifetime risk of sarcoidosis is 2.4 % for African Americans and 0.85 % for American Whites [11]. The wide variation in these estimates presumably reflects differences in diagnostic labelling 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's syndrome (an acute and self-limiting form of sarcoidosis characterized by bilateral hilar lymph adenopathy, erythema nodosum/arthralgia and uveitis) in Scandinavians, lupus pernio (a chronic purplish indurated lesion seen mainly on ears, cheeks, lips and nose) in Puerto Ricans. Rare lung disease may also display regional variation. This is the case of Hermansky-Pudlak syndrome, a disease characterized by oculo-cutaneous albinism, a bleeding diathesis, and diffuse lung fibrosis (prevalence of 1 in 1,800 in Puerto Rico but only isolated case reports and small clusters in the rest of the world) [12, 13], and in pulmonary alveolar microlithiasis, a disease associated with sand-like particles in the lung, which occurs predominantly in Japan and Turkey [14].

Identify Causation/Disease Pathogenesis

The cause and pathophysiology of rare diseases are largely unknown. Up to 2009, one or more responsible genes were identified for only 2,105 of the over 6,000 rare diseases listed on the Orphanet website (www.orpha.net). The environment, including exposure to microorganisms, may also play a role, particularly in the presence of a patient's compromised immune system, making these disorders varied and complex. However, for the vast majority of these diseases, no research is being conducted into causation, which, in turn, complicates both diagnosis and research into interventions. In fact, for some entities there are no guidelines and current recommendations are based on very limited data and expert opinion.

Unclear/Imprecise Definition

Rare lung diseases are often difficult to diagnose because of inconsistent case definition. For instance, hepatopulmonary syndrome is a rare disorder defined by a triad of liver disease, intrapulmonary vascular dilatation, and abnormal gas exchange [15]. It may also be a rare complication of more common chronic liver disease, such as liver cirrhosis [16]. However, the definition of "abnormal gas exchange" has varied widely in the published literature [17]. Diverse diagnostic thresholds lead to variable prevalence, render it difficult to compare studies and complicate patient recruitment owing to confused selection criteria. Expert consensus statements and guidelines – not available for most rare diseases – would undoubtedly facilitate consistent disease definitions.

Disease Complexity

Pulmonary involvement from 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 germ line mutations in the *FLCN* (folliculin) gene located on chromosome 17p11.2, and characterized by skin fibrofolliculomas, multiple lung cysts, spontaneous pneumothorax, and renal cancer [18]. BHD-associated skin lesions may also include angiofibroma, which are more typically associated with tuberous sclerosis. In turn, tuberous sclerosis may manifest with pneumothorax (caused by rupture of lung cysts), and renal cysts or tumours and should therefore be considered in the differential diagnosis of BHD [19]. The diagnosis of BHD 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

Pulmonary alveolar proteinosis (PAP) is a rare condition characterized by the accumulation of surfactant within alveolar macrophages and alveoli. Based on recent data from basic science and translational research, PAP is now recognized as a highly heterogeneous syndrome belonging to a much larger group of disorders of surfactant production (A) and clearance (B) – collectively known as *disorders of surfactant homeostasis*. The former group include mutations in genes encoding surfactant proteins (SP)- B, and C [20] or proteins involved in surfactant lipid metabolism (i.e., ABCA3; [21]). Conversely, PAP syndrome belongs to the second category of disorders, and can be either idiopathic (primary PAP) or secondary (to inhalation of dust, such as silica, or underlying immunologic and hematologic diseases that alter macrophage function). Primary PAP appears to be an autoimmune disorder associated with the presence of neutralizing autoantibody directed against granulocyte macrophage colony-stimulating factor (GM-CSF; [22]). Deficient GM-CSF activity, in turn, results in defective alveolar macrophages that are unable to maintain surfactant homeostasis and display defective phagocytic and antigen-presenting capabilities [23]. Recent studies suggest that neutrophil dysfunction, contributes to the increased susceptibility to lung infections observed in PAP [24]. Data from animal models suggest that the phenotypic and immunologic abnormalities of PAP can be corrected by GM-CSF augmentation therapy, although the effectiveness of this approach is not obvious since patients have autoantibodies (whose origin remains a mystery) to GM-CSF rather than abnormal protein levels.

Despite the complexity of the different diseases that are included in the "disorders of surfactant homeostasis", this is a wonderful, if sadly uncommon, example of the way in which basic, animal-based, research can digitate so effectively into an understanding of the basis of human disease that in turn stimulates the development of an effective, novel, treatment strategy.

Lack of Access to Correct Diagnosis

Delay in Diagnosis

For many individuals who develop a rare disease, the period between the emergence of the first symptoms and the appropriate diagnosis often involves unacceptable and highly risky delays, as well as in many instances the wrong diagnosis being made that leads to the administration of inappropriate and sometimes dangerous treatments. A survey of the delay in diagnosis for eight rare diseases in Europe has been conducted by EURORDIS (European Organization for Rare Diseases) in collaboration with 67 European rare disease organizations [1]. The main findings of this survey were that 25 % of patients had to wait between 5 and 30 years from early symptoms to confirmatory diagnosis of their disease. Before receiving a confirmatory diagnosis, 40 % of patients first received an erroneous one and others received none. Twenty-five percent 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 misdiagnosis include clinical worsening of the patient's health – even leading to the death of the patient – and loss of confidence in the healthcare system. This is utterly unacceptable – imagine if this had occurred to a member of one's own family – and cannot 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 diseases [25]. 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 centres 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 while from a clinical perspective they contribute to patient morbidity. For instance, most patients suffer episodes of pneumothorax before being diagnosed with LAM. In addition, misdiagnosis not only leads to inappropriate – and ineffective – treatments but also to unnecessary risks (pregnancy or air travel in the case of LAM). Similarly, in patients with Hermansky-Pudlak syndrome, invasive procedures should be avoided if at all possible, because of the patient's tendency to bleed. In this 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 likley to fall victim to an erroneous diagnosis.

Challenges but Not Negativity

These challenges should not be seen as insuperable and in some cases have been successfully overcome (see below) but they do illustrate how links between basic and clinical

biology can be made, and should continue to be made, if the forward momentum is to continue, and how this fusion can be used to benefit the disease in question. This requires a clear appreciation of the fundamental pathological aspects of the disease in order to identify how to best impact on the pathology; 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 review on the bleomycin model of lung fibrosis as a purported "model" for IPF and how this has in general failed to provide any novel therapy for the disease in question) [26].

Some Success Stories

The challenges to making progress in the approach to and treatment of rare and orphan lung diseases can be overcome despite the many problems that we have outlined. Two examples are illustrative of the way clinical science, clinical diagnostic precision and multinational networking can combine to result in therapeutic benefit: idiopathic pulmonary fibrosis and LAM.

Idiopathic pulmonary fibrosis (IPF) is a disease that fulfills the criteria for being both a rare and an orphan disease [27]. Until the beginning of the current millenium, little effort had been put into the search for novel effective therapies. During the last decade, however, there has been a significant momentum shift in the numbers of large clinical trial of novel therapy [28–45]. These have been made possible by a combination of good science that has allowed a better understanding of disease pathogenesis to emerge, combined with tighter definitions that, taken together, have provided confidence in targetting the important pathological processes in groups of individuals with well-defined disease using novel agents that have been and continue to be emerging from pharmaceutical industry pipelines. Although many of these studies were negative, four of these resulted in advances in management of this attritional disease process. The contribution of patient foundations has also been hugely supportive.

In the same vein, a better understanding of the processes that underpin LAM [46], together with the emergence of a strong international network of clinicican-scientists and supported by another important patient organisation (see below) has resulted in the completion of a successful study of an agent, sirolimus, that was predicted to block key mechanisms unearthed by clinical research and that demonstrated stabilisation of lung function and improved quality of life [47].

Both of these examples illustrate that just because a disease is rare it need not remain orphan without hope of progress in treatment and disease management. It does, however, require a team approach and an equipoise in collaboration that transcends individual interests to result in a successful outcome. These two examples may be considered to provide a template for other rare and orphan diseases that require the same sort of concerted organisation that would attract research funding together with pharmaceutical company interest in developing focussed therapies.

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

One of the more fundamental obstacles to undertaking research in rare disease is the absence of sufficient patient numbers to study disease causation, susceptibility and disease phenotype complexity, that would allow insights into the mechanisms of disease to be obtained, which would provide the basis for strategies to block the pathological pathways. Once these numbers can be gathered, expertise improves, patients become aware of research into their disease and this then becomes an iterative process of knowledge acquisition. To improve patient numbers is the start point and there are a number of strategies that could be employed to facilitate the process.

The Importance of Patient Organizations

Patient organisations are vital in rare disease by forming 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 further guidance. In this way 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 diseases, by educating and supporting patients and families. The LAM foundation illustrates the impact of patient-parent advocacy groups on basic and clinical research into rare diseases that have a significant impact on the lung.

Until recently, a diagnosis of LAM was a medical anomaly, and a patient who received this diagnosis had little cause for hope due both to 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 patho-biology of the [48] disease, and we now know that LAM results from the aberrant proliferation of smooth muscle-like cells ("LAM cells"), that infiltrate organs, especially the lungs and the kidneys, via the lymphatics [49, 50]. With increasing understanding of the disease, clinical trials not only became possible but also productive [47]. 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, patients contribute their personal insights, biologic samples as well as dedication and courage as they put themselves at risk in clinical trials of potential treatments for their rare disease. In turn, the results of the clinical trials may lead to more focused basic research in what can be referred to as "bench to bedside and back" research strategy. Other organisations, including the Raynaud's and Scleroderma Association in the UK and the Pulmonary Fibrosis Foundation in the US, have similar templates that combine education, support, and research in their drive for better treatment for patients.

Patient organizations have also been a huge motor in the development of enzyme replacement therapies 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 its first 3.5 years, the network successfully conducted 18 clinical trials involving 900 patients [51]. Several potential molecular targets and experimental therapies that may be appropriate for testing in clinical trials have been identified so far. Some of these drugs are Food and Drug Administration (FDA)-approved or in development for other indications. Finally, patient organizations are essential in order to identify specific medical unmet needs, which in turn represent a main driver of research. In this regard, a study conducted by EURORDIS in 2009 showed that funding from patient organizations is mainly focused on basic science, while they consider public funding for clinical, diagnostic and therapeutic studies (http://www.eurordis.org/content/survey-patient-groups-research).

National and International Networks

Increasing the sample size of studies on rare lung disease requires collaboration among research centers. This is essential in order to build up patient registries and databases, which, in turn, are vital in order to assess the feasibility and facilitate the planning of appropriate clinical trials and to support the enrolment of patients. In addition to building meticulous datasets, this approach would also serve to limit overlapping and competitive research efforts, which are particularly challenging in rare lung diseases, where both patients and resources are limited and often, therefore, wasteful of resource by reduplicating 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 the quality of different data sources and regulations across countries.

One other approach would be to export the expertise rather than import the patients. With the Internet and the explosion in social networks, it should not be long before research and even diagnoses can be developed at a distance. Certainly major funding bodies internationally need to invest in such 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 undertake studies of large patient cohorts, trials can be designed using methodology that allows efficacy and safety to be balanced even with small patient numbers [52–56]. Such studies of novel therapy that utilise small numbers of patients, provided that they are well-designed studies, can result in regulatory approval despite the small numbers [57]. Further impetus could be provided by the creation of registries that would capture accurately the true prevalence and incidence of the rare diseases across nations; not a trivial task as evidenced by the flaws and difficulties observed with some of the extant registries. This requires significant resource input into staff to serve and develop the capturing and audit of data. A second advance requires the continuing development of sensible guidelines that would allow the harmonization of diagnostic criteria and management principles across nations.

End Points for Trials – Getting Them Right When Numbers Are Small and Change Is Slow

Clinical trials in the field of rare diseases suffer from a number of weaknesses: (1) Because of the small number of participants, a statistically significant benefit may be difficult to reach; (2) Clinical trials are often too short regarding the natural history of a disease; (3) How to define benefit in disorder where there are often no well-defined and validated markers/surrogates for monitoring disease progression and treatment responses. As a result, only 57 % of approved orphan drugs have been tested in a randomized clinical trial before approval [58]. Furthermore, rare diseases are

frequently diagnosed and managed in childhood, thus representing a challenge for clinical studies, since trial approval for research in children, especially in some countries, can prove problematic and/or very slow.

Orphan Drug Development

The first stage in drug development consists of research into the mechanism and pathogenesis of a particular 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 the majority of rare diseases – thus the lack of possible pharmaceutical targets – and the scarcity of animal models, which at best often represents only partially what is observed in humans, are huge obstacles to preclinical studies and orphan drug development. In turn, the scarcity of funds invested and of human resources devoted to investigating rare diseases explains the difficulty faced by pharmaceutical companies to invest in this area. Further, for some conditions clinical trials need to be multinational owing to the limited existing experience at national level as well as the small number of patients affected by the same rare disease. Additional difficulties come from the fact that national clinical trial registration authorities may be unfamiliar with clinical trials in small populations. All these hurdles, combined with the estimated low return on investment due to very small markets and costly drug development, discourage the pharmaceutical industry and prevent it from developing drugs for rare diseases, despite the huge unmet medical needs.

However, there has been some important progress in regard to drugs research and development that has eased the pathways to getting drugs developed and approved in rare disease [59–63]. These include: regulatory and economic incentives for industry to develop drugs for rare disease via the orphan drugs acts; the recognition by regulatory agencies of the very individual nature of problems encountered in demonstrating efficacy of novel therapies in rare diseases and how to determine efficacy 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 Centres

Who should or is able to take a broad clinical perspective on the needs of patients affected by rare diseases? Given the number and diversity of these disorders, it is impossible that community physicians have knowledge about all of them. While the *optimum* for the general lung specialist would be a specific training including the study of rare diseases, at this time referral to centres 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, and nephrologists as well as 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 key to delivering proper care in rare disorders and can be only found in dedicated referral centers. This, in turn, allows patients 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. Cystic fibrosis is now included in neonatal screening programs in several countries and genetic counseling and support for parents of children diagnosed at birth occupy an important place [64]. This model now needs to be reproduced for other disorders.

These challenges to rare lung disease research are highlighted by a consideration of the continuing problems encountered in an area where, although the disease is classified as "rare", there have been successful efforts in international collaborations that have resulted in the development of treatments that have been demonstrated to have an impact on disease outcome – idiopathic pulmonary fibrosis. In this disease, in which large populations have been gathered across the globe that have allowed many clinical trials of novel therapy to be undertaken, there is still animate debate on what minimum investigation(s) need to be done to provide a confident diagnosis, whether any drugs actually do have an impact on disease and which end-points should be used to test efficacy of novel therapies. If the "experts" cannot achieve universal agreement on this most studied if relatively rare disease, what hope for the less common disorders? Certainly there will be challenges but with strong collaborations of individuals who share the ultimate goals, the IPF experience should not necessarily be the inevitable outcome of efforts in these less common disorders.

Looking to the Future

In addition to exploring areas where short and medium term progress can be made there is a requirement for a long term vision. This must include attention to education. Primary care and secondary care providers need to be aware of the range of rare diseases, patients need education and guidance on the implications of the disease that they have and where they can reach out for information that does not leave them truly orphaned and disenfranchised. Most importantly future generations of doctors need to have developed a lower index of suspicion for rare diseases. This can only be achieved by the creation of structured training for medical students that

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, certainly within Europe, which would have the added advantage of enhancing the opportunities for national and international collaborations in the future if there was a uniformity of teaching in the field.

The Arguments for Progress

Economic Burden

The burden of rare diseases in terms of suffering and human life loss is enormous. Likewise, though difficult to estimate, the economic load of rare diseases is massive. With a prevalence of at least one to two million people and conservative approximation of average yearly healthcare costs of 5,000$ per patient, the annual total cost in the US 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 healthcare visits are usually required to make the correct diagnosis, which, in turn, results in greater expenses, unnecessary tests and missed opportunities for early intervention.

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, can be costly or even dangerous by delaying access to accurate treatments and translate into an increase of expenses and a waste of resources for the healthcare 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 diagnosis, understanding or treatments of just some of the estimated 6,000–7,000 different rare diseases, would substantially reduce costs for healthcare systems. A patient affected by a rare disease, when properly treated, stops being a consumer of irrelevant tests or ineffective treatments or superfluous hospital admissions.

Patients Deserve Better

The low prevalence of rare diseases means that the numbers of patients who are affected are small or very small; those affected, therefore, feel particularly isolated. The isolation felt by these patients is not only geographical but also means marginalization within society at large and within healthcare systems designed for common diseases. 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 still unknown, which makes diagnostic methodologies and therapies difficult to develop. In turn, this aggravates patients' vulnerability and disadvantages them relative to the rest of society and to patients affected by more common diseases.

The Goal of Clinical Research in Rare Disease

Rare lung diseases are often chronic and debilitating, and, once diagnosed, may require unconventional, expensive and long-term treatments. This is the case of subcutaneously administered granulocyte macrophage colony-stimulating factor for pulmonary alveolar proteinosis and alpha-1 antitrypsin replacement for hereditary emphysema, for example. 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) signalling 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 [47]. Another example of targeted disease management includes glucocerebrosidase therapy for Gaucher's disease – the most prevalent lysosomal storage disorder.

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 of rare lung diseases but much work remains to be done. Most of them 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 (Fig. 2.1). In addition, basic and clinical studies on rare lung disorders are also likely to improve our understanding of physiologic and pathologic processes as well as

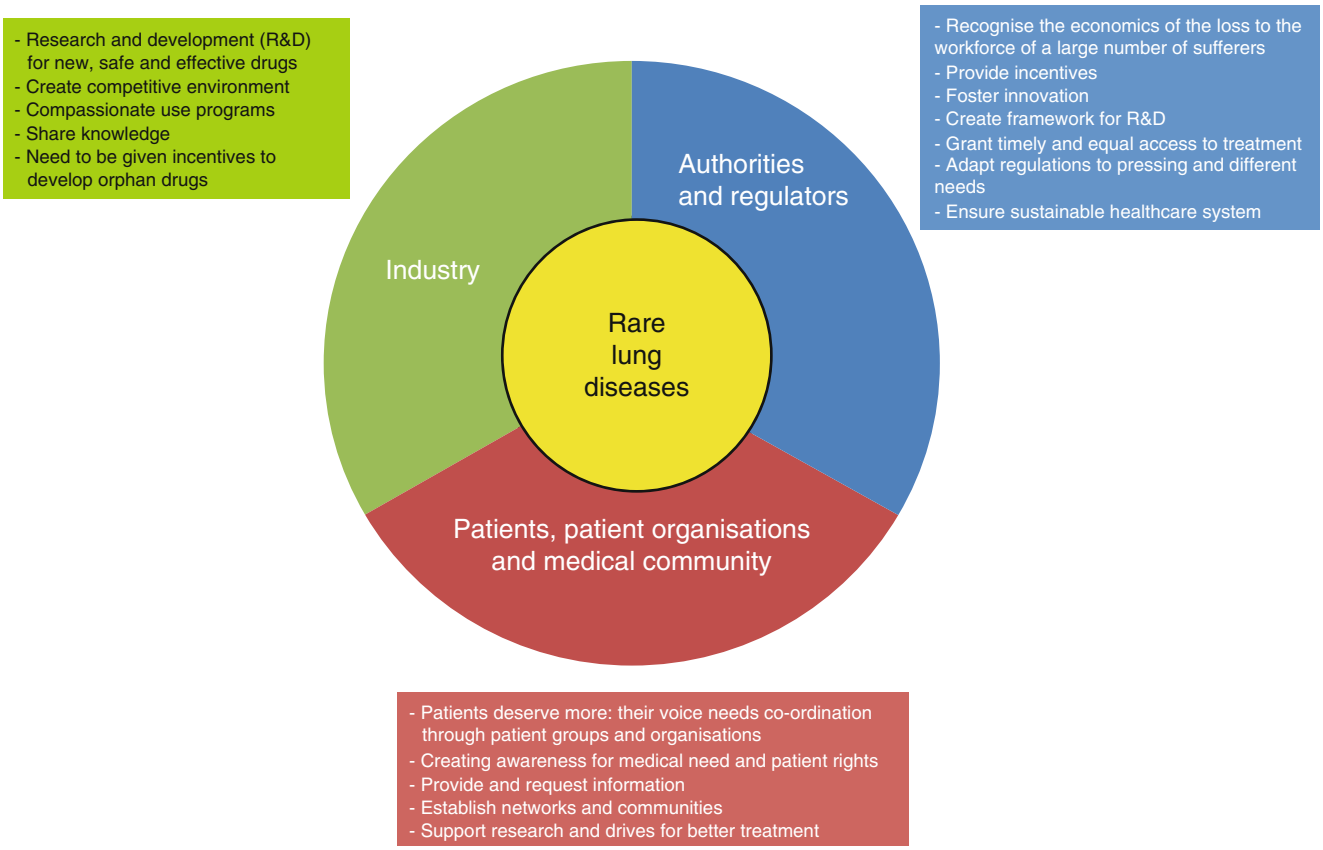

Fig. 2.1 A road map for success in rare disease: a call for organisation and harnessing resource

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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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 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 often is associated with outbreaks of infection (especially, respiratory syncytial virus) [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 histopathologic findings of the bronchiolar syndromes in adults and is orientated toward practical management. More exhaustive reviews can been found elsewhere [2, 3].

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Classification

Bronchiolitis is often confusing because the term describes both a clinical syndrome and a constellation of histopathologic 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); (2) a histopathologic classification, which includes two major morphologic types (proliferative bronchiolitis and constrictive bronchiolitis) [2].

Constrictive Bronchiolitis

Constrictive bronchiolitis is rare and is characterized by alterations in the walls of membranous and respiratory bronchioles that cause concentric narrowing or complete obliteration of the airway lumen (Fig. 3.2). Often these lesions occur without extensive changes in alveolar ducts or alveolar walls. The histopathologic changes range from subtle cellular infiltrates around the small airways to bronchiolectasia with mucus stasis, distortion, and fibrosis or total obliteration of the bronchioles. Patients with constrictive bronchiolitis often experience progressive obstructive lung disease, e.g., following inhalational injury. The chest imaging studies may be normal. It is useful to further divide constrictive bronchiolitis into five main groups: (1) cellular bronchiolitis, (2) follicular bronchiolitis, (3) diffuse panbronchiolitis, (4) respiratory (smoker's) bronchiolitis, and (5) cryptogenic constrictive bronchiolitis.

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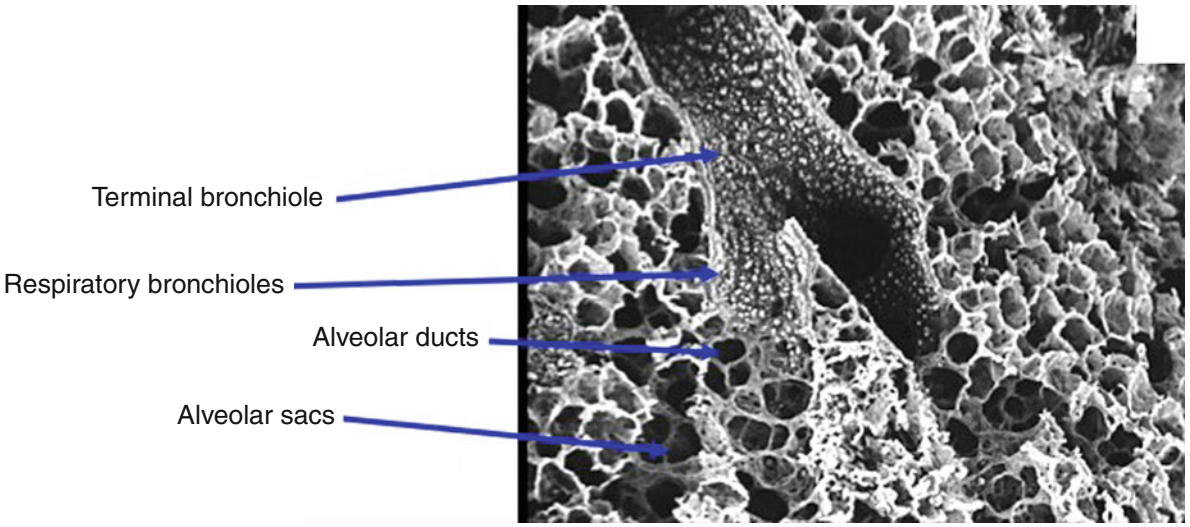

Fig. 3.1 Junctional area between the purely conductive airways and the respiratory portion of the lung. The terminal (nonrespiratory) bronchiole has a continuous cuboidal epithelium, whereas alveoli open off the respiratory bronchiole (Courtesy of Marco Chilosi, MD, Dipartimento di Patologia, Università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

Table 3.1 Clinical syndromes associated with histologic 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., fertilizer 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, trichlorethylene, hydrous magnesium silicate, stearate of zinc powder)
	Organic dusts	
	Mineral dusts	
	Volatile flavoring agents	
Postinfectious		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 panbronchiolitis
	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

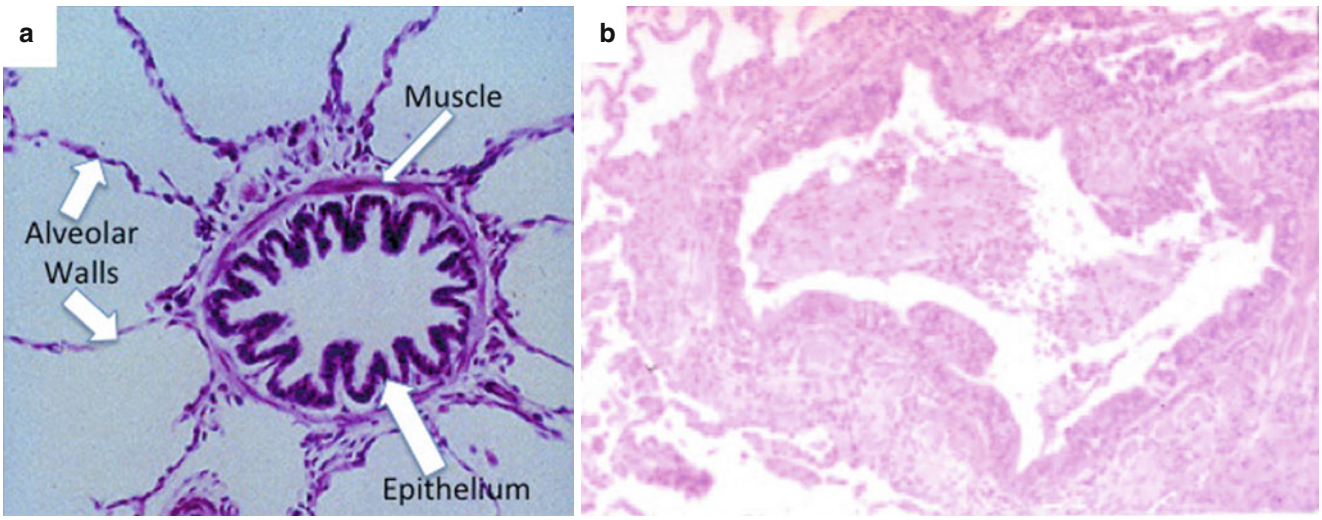

Fig. 3.2 (**a**) Photomicrograph of normal small airway. (**b**) Constrictive bronchiolitis. Photomicrograph of lung biopsy specimen shows bronchial smooth muscle hyperplasia, thickening and mild scarring of the bronchiolar wall, and scarring of the adjacent alveoli

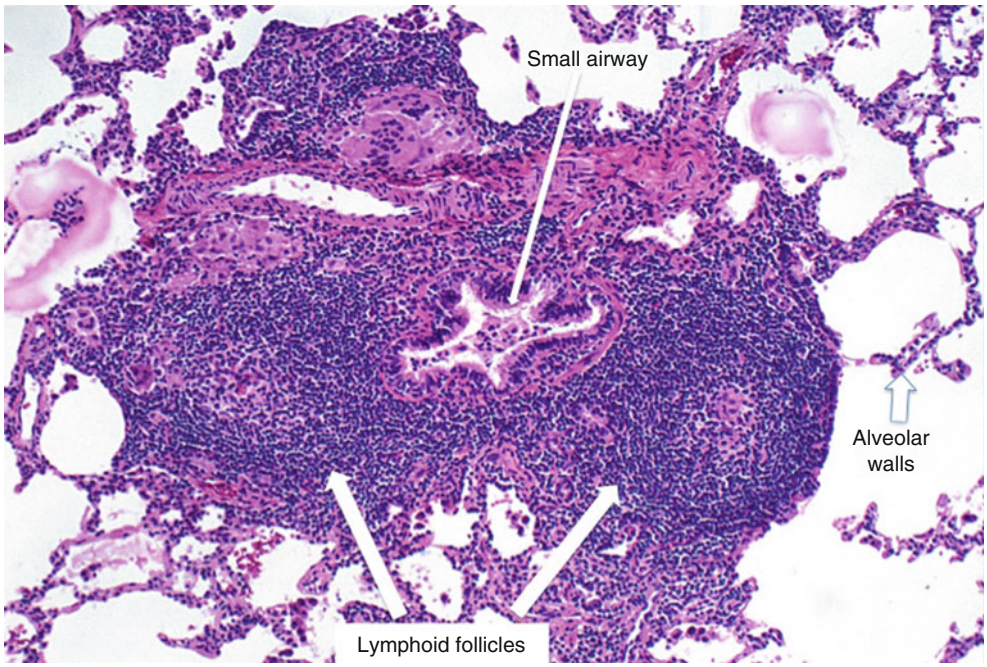

Fig. 3.3 Follicular bronchiolitis. Prominent lymphoid follicles adjacent to and impinging on the distal airway (Courtesy of Jeffrey L Myers, MD, Department of Pathology University of Michigan)

Cellular Bronchiolitis

Cellular bronchiolitis is a descriptive histologic term that refers to inflammatory infiltrates that involve the lumen, the walls of bronchioles, or both [2]. 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. 3.3) [4]. Most cases occur in patients with connective tissue disease (e.g., rheumatoid arthritis and Sjögren's syndrome) [5]. Other associations include immunodeficiency syndromes, familial lung disorders, chronic infection, and a heterogeneous group of patients with a hypersensitivity-type reaction.

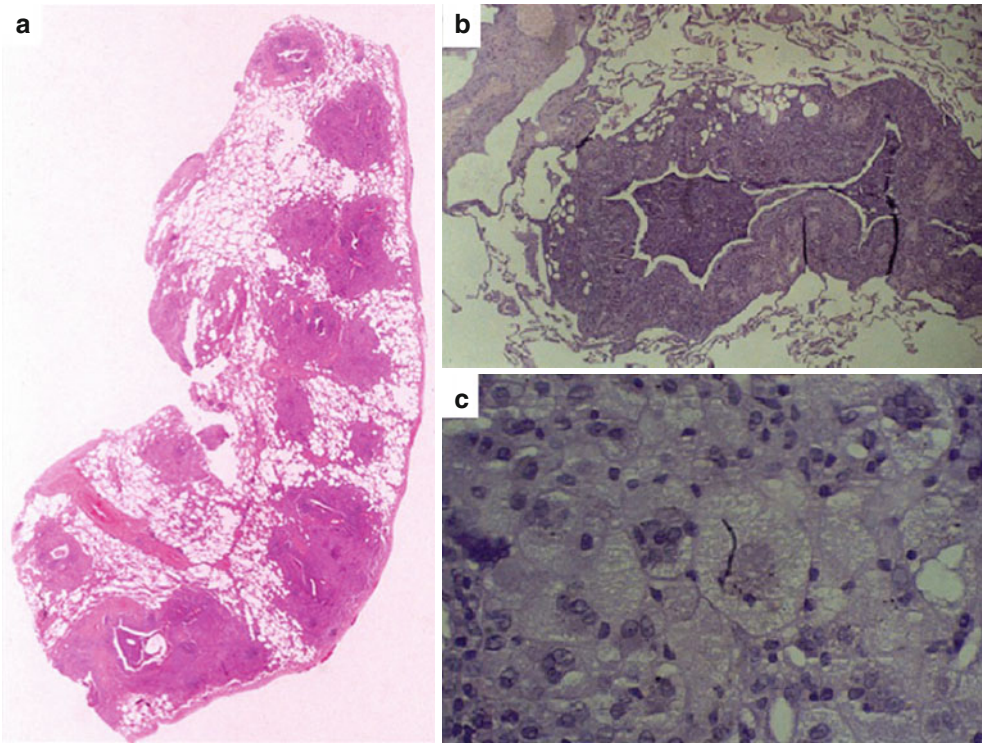

Fig. 3.4 (**a**) Diffuse panbronchiolitis. Scattered nodules are seen at low power. The primary lesion is an inflammatory process of the respiratory bronchioles with marked associated foam cell accumulation (Courtesy of Jeffrey L Myers, MD, Department of Pathology University of Michigan). (**b**) Inflammatory 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)

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 [6]. 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 infiltrate with peribronchiolar fibrosis and an absence of granulomas [7]. The typical patient is a middle-aged woman (40–50 years old) with a chronic nonproductive cough. Many cases are thought to be characteristic of hypersensitivity pneumonitis on clinical grounds, although no specific antigen has been identified [8]. Unlike hypersensitivity pneumonitis, the percentage of lymphocytes on bronchoalveolar lavage is less than 40 % [7]. 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. 3.4). These findings often produce nodular lesions [6]. This distinctive form of small airways disease is relatively common in Japan, China, and Korea; it is rare in other parts of the world [9].

Proliferative Bronchiolitis

Proliferative bronchiolitis is characterized by an organizing intraluminal exudate and is extensive and prominent in organizing pneumonia [10]. The intraluminal fibrotic buds (Masson bodies) are seen in respiratory bronchioles, alveolar ducts, and alveoli. Proliferative bronchiolitis is most frequently associated with diffuse alveolar opacities on chest radiograph and CT scan. A restrictive defect is found on pulmonary function testing.

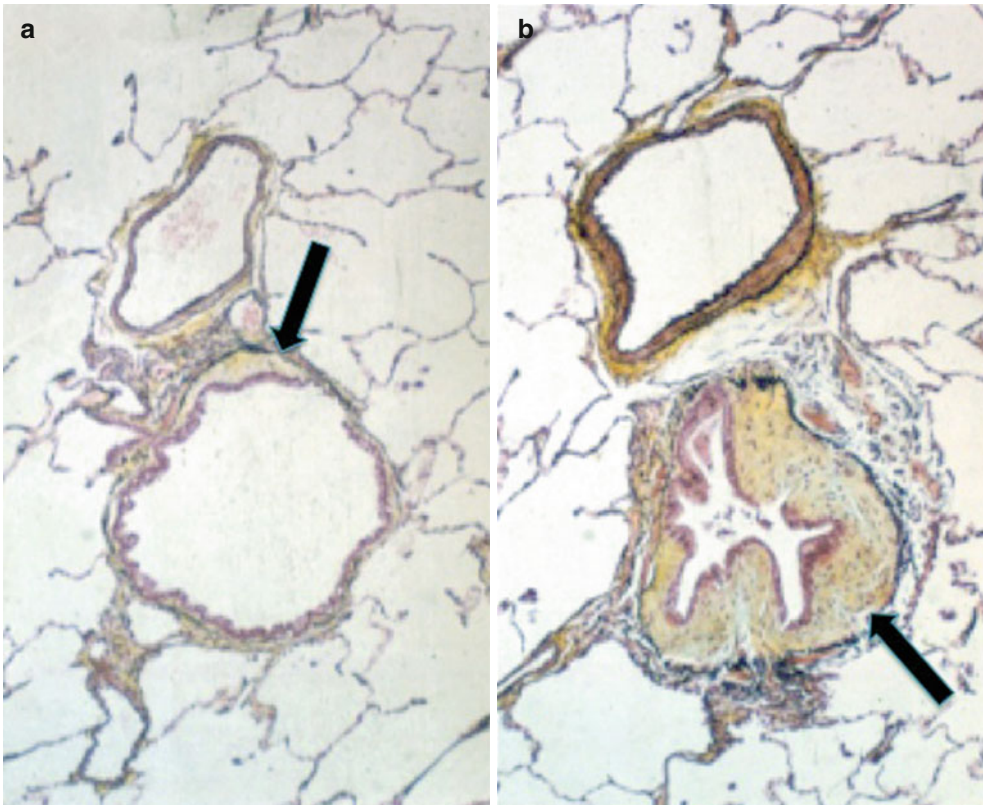

Fig. 3.5 (**a**) Slightly dilated bronchiole with minimal fibrosis (*arrow*) and normal intervening lung (Pentachrome stain; ×156 original magnification). (**b**) Severe concentric narrowing of the bronchiolar lumen due to fibrosis (*arrow*) (Pentachrome stain; ×156 original magnification) (Adapted from: King [2])

Diagnosis

Patients, who present with the 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 ago 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/minute, 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 lung. 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. 3.5). 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 [3]. 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).

Box 3.1
Diagnostic Criteria

A. **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:

- Preceding upper respiratory symptoms, including rhinorrhea and fever
- Signs/symptoms of respiratory distress: cough, dyspnea, tachypnea, wheezing, inspiratory crackles and a midinspiratory squeak.

B. 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.

- **Chest Imaging studies**
  - **Chest x-ray** is obtained most commonly to rule-out bacterial pneumonia and to assess disease severity. The chest radiograph is of limited usefulness in the diagnosis and note 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: 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.
- **Pulmonary function testing:**
  - Constrictive bronchiolitis: normal or show obstructive changes with air trapping.
  - Proliferative bronchiolitis: a restrictive pattern is the common.
  - Diffusing capacity is usually reduced in both types
  - Resting hypoxemia is frequently present in both patterns.

C. **Lung biopsy–**Open or thoracoscopic lung biopsy is commonly required to make a definitive diagnosis.

Chest Imaging Studies

The chest radiograph is of limited usefulness in the diagnosis and follow-up of patients with bronchiolitis–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 [11].

Inspiratory and expiratory CT scans are most useful in identifying findings consistent with bronchiolitis (Fig. 3.6). 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 [11–17]. Cylindrical bronchiectasis is frequently associated with bronchiolitis [14]. Expiratory CT scans are important in the assessment of air trapping, which is a characteristic finding of partial airway obstruction [18]. Small peripheral centrilobular nodular parenchymal densities are nonspecific indirect signs of small airways disease [17].

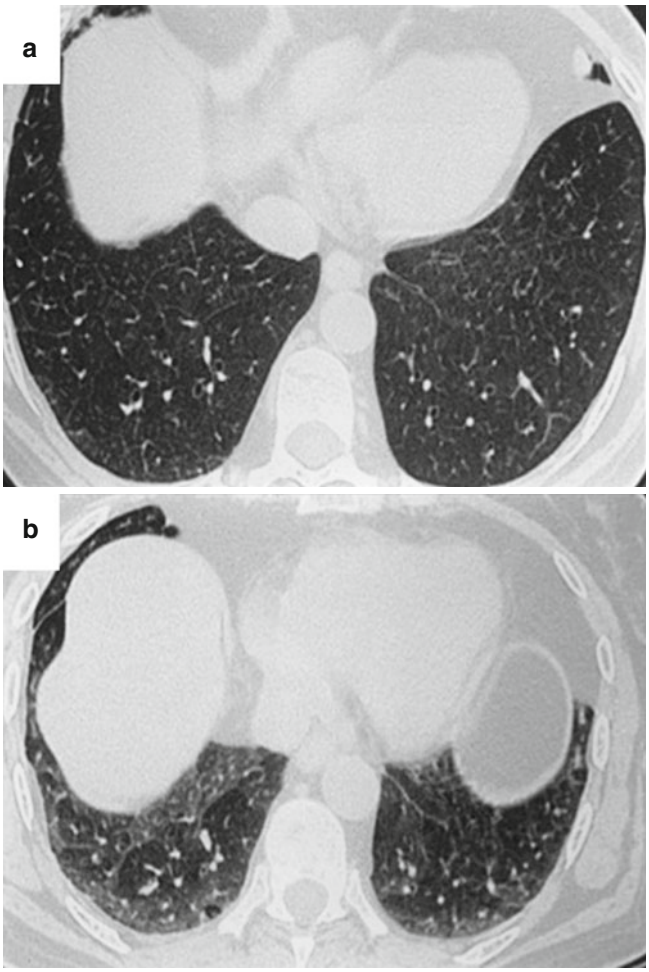

Fig. 3.6 (**a**) Normal inspiratory high resolution CT scan. (**b**) Expiratory high resolution CT scan showing characteristic mosaic pattern with areas of decreased and increased attenuation reflecting air trapping. Note that areas in which lung density remains virtually unchanged are indicative of substantial air trapping

These hazy nodular opacities appear as focal rounded areas of increased ground-glass attenuation, measuring less than 1 cm in size [17]. 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 [16]. The findings are asymmetric and vary over time.

Pulmonary Function Testing

In constrictive bronchiolitis, lung function may be normal or show obstructive changes with air trapping. In proliferative bronchiolitis, a restrictive pattern is the 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, open or thoracoscopic lung biopsy is required to make a definitive diagnosis [2, 3]. Transbronchial lung biopsy is often inadequate for diagnosis. Tissue confirmation may not be necessary in patients with a clear predisposition and typical HRCT. The histopathologic 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 [3].

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 [19]. After recovery from the acute illness, or in patients with no symptoms following exposure, recurrence or new onset of clinical illness 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 thought 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

Pathologic 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 has been reported [20, 21]. The clinical relevance of the lesions found in these subjects awaits better definition. Nevertheless, the development of airflow obstruction, rather than the classic restriction, is increasingly recognized 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 disease in workers exposed to flavoring chemicals at microwave popcorn plants and flavoring production plants [22–25]. Chest radiographs showed hyperinflation in several cases. HRCT findings included diffuse cylindrical bronchiectasis and a mosaic pattern suggestive of air trapping [26]. This pattern suggests a predominant constrictive bronchiolitis pattern. Pathology consistent with obliterative bronchiolitis has been found [24].

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 associated primarily with M. pneumoniae; however, a number of other viruses (e.g., RSV, especially in the elderly) and bacterial agents have been identified [2]. 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 clinicopathologic 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 suggest 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 clinicopathologic syndrome that is found in middle-aged women who have a nonproductive cough, shortness of breath, or other nonspecific chest complaints, usually of relatively short duration (6–24 months) [27–30]. Few cases have been reported, and it is not entirely clear that 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 chronic cough and progressive dyspnea. Most cases have not been smokers. A history of possible inhalational exposures has been found in the majority of cases [7]. 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) [7, 8, 31–35]. 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 lung parenchyma [34]. Pulmonary architectural reconstruction, metaplastic bronchiolar epithelium (honeycomb lung formation under microscope), and subpleural focal pulmonary fibrosis was also seen.

Connective Tissue Diseases

Bronchiolitis occurs infrequently among the 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 midinspiratory squeak. A positive rheumatoid factor is present, often at high levels (1:640–1:2,560). Most patients have a chronic course. The prognosis is poor, with early deaths reported [36].

Organ Transplantation

"Bronchiolitis obliterans syndrome," manifested by progressive airflow obstruction, is a frequent noninfectious post-transplantation respiratory complication. The incidence of bronchiolitis obliterans among single-lung recipients is approximately 20 %; in double or bilateral sequential single-lung recipients, the incidence is 12 % [37]. 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 [38–41]. 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 lung 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. 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 as well. 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 HLA-Bw54 (63 % frequency) [42]. Because HLA-Bw54 or its related haplotype are confined primarily to some mongoloid races (e.g., Japanese, Chinese, and Koreans), the genetic and ethnic background observed with this unique syndrome may be explained [43]. Environmental factors also appear important, because the disorder is very 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 [44].

The 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 fashion, 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 [2, 3]. Macrolide antibiotics are commonly used in the long-term management of bronchiolitis based largely on their success in improving symptoms, lung function, and mortality in patients with diffuse panbronchiolitis (see below) [45]. 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) so should be discontinued [2, 3]. 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 [46]. 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, 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 [48]. 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 approached 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) have been used for most patients. Erythromycin impairs neutrophil chemotaxis, neutrophil superoxide production, 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.

Follicular Bronchiolitis

Follicular bronchiolitis is usually treated as part of the underlying disease, whether it is a connective tissue or associated with immunodeficiency [3].

Airway-Centered Interstitial Fibrosis

The optimal treatment for airway-centered interstitial fibrosis is not known. Glucocorticoid therapy has been tried with limited success [3].

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) [2, 3]. 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, given 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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"Diffuse Bronchiectasis of Genetic Origin"

4

Jane S. Lucas and Katharine C. Pike

Introduction

Bronchiectasis is a disorder of the segmental and sub-segmental bronchi that is characterised by destruction of the elastic and muscular elements of the bronchial walls resulting in bronchial dilatation and chronic infection. Predisposing conditions are those associated with bronchial obstruction, inefficient pulmonary toilet, and susceptibility to chronic or recurrent infection. In developing countries, bronchiectasis remains a frequent complication of acute infection. Post-infectious bronchiectasis is becoming very rare in western countries due to the availability of antibiotics and immunisation, particularly against pertussis and measles [1]; bronchiectasis in adults who developed disease in early childhood predating these developments is not, however, uncommon [2]. Focal bronchiectasis may occur in the context of isolated bronchial obstruction due, for example, to an inhaled foreign body. In the developed world, diffuse bronchiectasis is typically found in association with underlying disorders of mucociliary clearance, immune defence or bronchial anatomy. A number of genetic disorders are known to predispose to bronchiectasis and it is likely that some less well characterised heritable disorders underlie a proportion of cases currently regarded as diffuse idiopathic bronchiectasis.

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Pathophysiology and Presentation

Recurrent or chronic infection results in repeated plugging of the airway, recruitment of inflammatory cells and release of inflammatory mediators and cytokines; this, in turn, can cause permanent structural airway changes [3, 4]. As a consequence of the unopposed traction exerted by the surrounding lung parenchyma, destruction of the elastic and muscular elements of the bronchial walls causes airway dilatation. Accumulation of purulent secretions ensues. In the 1980s Cole proposed the 'vicious cycle' mechanism of on-going and self-perpetuating damage in bronchiectasis [5]: once airway dilation occurs, mucociliary clearance is impaired and the airway becomes at greater risk of repeated infection and further damage.

The age of onset of symptoms is variable, and depends on the underlying cause. For example, the majority of infants with primary ciliary dyskinesia have respiratory symptoms from the early neonatal period due to congenital impaired mucociliary clearance. Children with antibody deficiencies may not present until passive maternal immunity subsides. Early investigation of persistent cough is essential if interventions are to be implemented before irreversible bronchiectasis ensues.

Persistent cough is a cardinal feature of bronchiectasis; cough is generally described as wet or loose although in the authors' experience parents will often incorrectly describe their child's cough as dry. The sputum is typically purulent during recurrent or persistent infections. Reduced exercise tolerance and increased work of breathing may be present, but these are generally associated with advanced disease or infective exacerbations. Haemoptysis is relatively rare in children [6] but is more common in adults with bronchiectasis.

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Haemoptysis may occur as a consequence of dilating airways encroaching upon bronchial blood vessels or as a result of bronchial artery proliferation in association with chronic inflammation [7]. The bleeding is generally mild, presenting as streaks of blood in the sputum, but can be massive and fatal. Chronic alveolar hypoxia can cause right-sided heart failure. Other complications of bronchiectasis include empyema and pneumothorax.

In the past bronchiectasis commonly presented with wasting and anaemia, alongside prominent crackles and clubbing [8]. Probably due to earlier recognition of less severe disease, this picture is less often seen today. Examination may be normal or may include crackles, wheeze, or chest deformity. Clubbing is reported to occur in approaching 50 % of patients with bronchiectasis [9], and is an important, but not sensitive, distinguishing feature in patients with symptoms of wheeze or cough otherwise suggestive of asthma [10]. Individuals with bronchiectasis may wheeze, but in contrast to people with asthma, this is almost invariably associated with *wet* cough.

Epidemiology

The introduction of immunisations against pertussis in the 1950s and measles in the 1960s contributed greatly to the decline of bronchiectasis, as has the decline of pulmonary tuberculosis and the general improvement in social circumstances. The introduction of sensitive high resolution computed tomography (HRCT) techniques in the 1990s, capable of detecting minimally symptomatic disease, makes it difficult to compare historical data with more recent estimates. Prevalence in UK adults from the Bedford region in the 1950s was estimated to be in the region of 1 per 1,000 [2], more recent estimates from the US suggest a prevalence of 4 in 100,000 rising to 3 in 1,000 in older adults [11]. Paediatric population-based calculations from the United Kingdom estimated hospitalisation due to bronchiectasis to be 50 per 10,000 population at the beginning of the 1950s reducing to 10 per 10,000 with the introduction of antibiotic therapy [12]. During the 1960s the incidence of bronchiectasis was estimated to decrease further to 1 case per 10,000 population [13]. Recent data from New Zealand suggest a prevalence in children under the age of 15 years of around 4 per 100,000 [14], whilst data from a tertiary referral centre in the north east of England suggest the prevalence this age group may be as high as 1 per 5,800 [10]. 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.

Bronchiectasis is particularly prevalent in children from certain indigenous subpopulations, including Pacific Islanders, Indigenous Australians and the Inuit community in North America [14–16]. Poor access to antibiotics and immunisations may partially explain these differences, although it is likely that genetic propensity may play a role [17, 18]. Certainly, children of consanguineous parents are at a disproportionately high risk of genetic causes of bronchiectasis [19]. Moreover, although environmental, immune or anatomical factors may explain the observation that non-CF bronchiectasis is more common and more severe in females, this too may have a genetic basis [20].

The most common genetic cause of diffuse bronchiectasis is cystic fibrosis (CF), the incidence of which is estimated to be 1 in 2,500 births in white Caucasians. Reports of primary ciliary dyskinesia (PCD) prevalence in European populations have varied greatly from 1 in 10,000 to 1 in 40,000 [21]. 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, leading to considerable under-diagnosis. A recent survey by a European PCD Taskforce suggested that PCD in children is under-diagnosed and diagnosed late, particularly in countries with low health expenditures [22]. The prevalences of other genetic causes of bronchiectasis are very low and are considered individually later it this chapter.

Genetic Causes of Diffuse 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 4.1). More rarely disorders of cartilage or collagen are the underlying cause.

Table 4.1 Examples of genetic causes of bronchiectasis

	Examples of known causes
Disorders of mucociliary clearance	Cystic fibrosis
	Primary ciliary dyskinesia
	Young's syndrome
	Alpha-1 antitrypsin deficiency
Primary immunodeficiency	
Hypogammaglobulinaemia	Common variable immunodeficiency
	X-linked agammaglobulinemia
	IgA deficiency
	IgG subclass deficiency
Neutrophil deficiency	Chronic granulomatous disease
	Schwachman-Bodian-Diamond syndrome
Innate immunity	Complement deficiency
Collagen disorders	Marfan syndrome
	Williams-Campbell syndrome
	Mounier-Kuhn syndrome
Other associations	Autoimmune disease

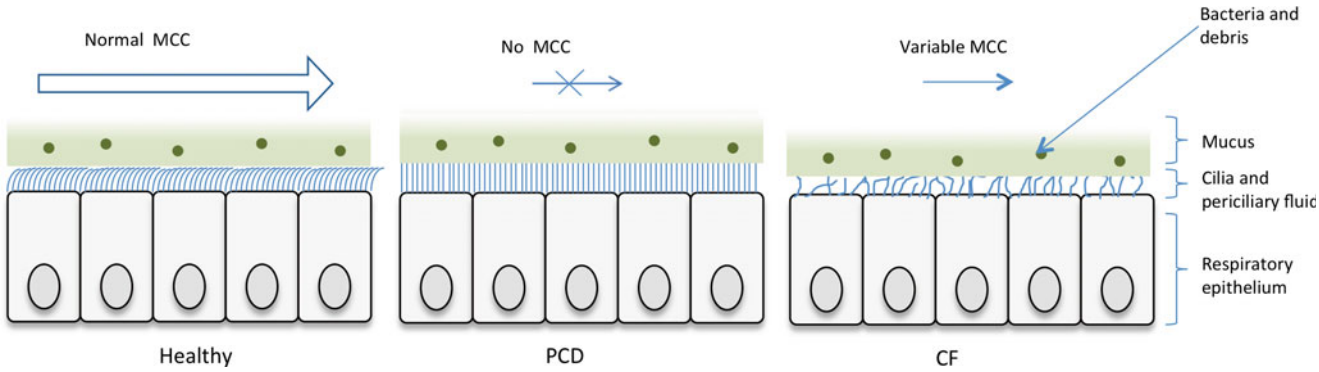

Fig. 4.1 In healthy persons, respiratory cilia beat in a coordinated sweeping pattern, which moves mucus and debris, including pathogens towards the oropharynx for swallowing or expectorating. In PCD, immotile or dyskinetic cilia do not beat effectively, and mucus and debris persist in the airways. In CF the inefficient mucociliary clearance is due to an abnormal periciliary fluid layer compromising ciliary beating, and viscous mucus which is resistant to clearance (Image provided by Robert Scott)

Disorders of Mucociliary Clearance

Ciliated respiratory epithelium lines the airways. The cilia, bathed in perciliary fluid, beat in a coordinated fashion at 11–18 Hz, to propel the overlying mucus along with particles and bacteria to the oropharynx where it can be swallowed or expectorated (Fig. 4.1). 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, with an estimated incidence of 1 per 2,500 live births in Caucasian populations. 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 on cell membranes. Mutations affect CFTR function by a variety of routes including complete loss of the protein, rapid breakdown of CFTR and surface expression of a dysfunctional protein. The most common mutation is ΔF508; a deletion of three nucleotides which results in loss of phenylalanine at the 508th position on the protein causing abnormal tertiary structure and rapid degradation with no apical membrane expression. A very large number of mutations (>500) have been identified in the CFTR gene, but a select group are more commonly associated with disease (e.g. G542X, G551D, N1303K). The prevalence of mutations differs between ethnic populations.

Abnormalities in CFTR cause abnormal ion transport regulation across the cell membrane. In the lungs this results in abnormal airway fluid. Dehydrated mucus is characteristically highly viscoelastic, and adheres to the cilia and airway 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. 4.1). 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 [23]. Bronchiectasis in CF predominantly affects the upper lobes initially, spreading to all lobes over time. The reasons for upper lobe predominance have been suggested to include aspiration, poor clearance by cough and poor lymphatic clearance to this region, although the disparity with PCD which tends to have worse disease in the middle lobe is difficult to explain.

Although respiratory disease accounts for the vast majority of morbidity and mortality [24]. CF is a multisystem disorder, with manifestations including meconium ileus, pancreatic insufficiency, steatorrhea, failure to thrive, liver disease, diabetes, nasal polyposis and sinusitis. Most cases present before the age of 2 years although later presentation, including in adulthood, is not unheard of particularly in individuals carrying mutations other than ΔF508 who are more likely to be pancreatic sufficient and less likely to have diabetes or pseudomonas colonisation [25]. Diagnosis of classical cases of CF is based on an abnormal sweat test (sweat chloride > 60 mmol/L). Supplementary investigations include CFTR mutations and abnormal transepithelial potential difference.

The majority of patients with CF are easy to diagnose early as they have classical lung disease ± pancreatic insufficiency associated with two CF associated CFTR mutations and an abnormal sweat test result (>60 mmol/l). A further group of patients with mild lung disease and pancreatic sufficiency is confidently diagnosed, often in adulthood, on the basis of a diagnostic sweat test and two disease causing mutations. The group that cause particular difficulty are

those with clinically milder phenotypes associated with a variety of equivocal outcomes from genotype and functional investigations (sweat test and nasal potential difference). This is a difficult and controversial area for clinicians and recently international consensus guidelines have been proposed to help in the diagnosis of patients with "CFTR dysfunction that does not fulfil diagnostic criteria for CF" [26]. These single organ disease states are becoming recognised as a spectrum of CFTR related disorders. Very many mutations have been identified in CFTR, but not all are associated with disease and it has been suggested that some only cause disease when interacting with certain environmental factors or other genes. Some patients present with two known disease-causing mutations, but an equivocal sweat test result. These patients generally have more severe lung disease than those with an equivocal sweat test and normal genotype, but they have milder disease than a patient with the same genotype and sweat chloride concentration >60 mmol/l. This highlights different phenotypes associated with a spectrum of test results, indicating the need to perform functional tests even in the presence of two mutations. It is probably appropriate to consider patients with mild CF-like disease associated with two mutations and a normal sweat test as an atypical CF variant. Another group that cause diagnostic uncertainty are those with only one CFTR mutation. These patients may have atypical CF. However the diagnosis of mild or atypical CF with equivocal CF results should only be made after all other causes of bronchiectasis have been excluded. It is prudent to keep the diagnosis under review as our understanding of CFTR related disorders evolves.

Primary Ciliary Dyskinesia

After CF, primary ciliary dyskinesia (PCD) is the most prevalent (1:10–40,000) genetically determined cause of impaired mucociliary clearance. PCD is inherited in an autosomal recessive pattern, and is characterised by chronic infection of the upper and lower airway [21, 27]. The impaired mucociliary clearance is a consequence of abnormal ciliary beat function which is usually [27], but not always [28, 29], associated with abnormal ciliary ultrastructure seen by transmission electron microscopy (Fig. 4.2a–d). Motile cilia are important in organ systems besides the respiratory tract, such as the embryonic node, sperm flagella (Fig. 4.2e), the female reproductive tract, and ependyma of the brain and spinal cord. PCD patients therefore often have extra-pulmonary symptoms caused by dysmotile cilia such as serous otitis media, infertility and rarely hydrocephalus. The cilia of the embryonic node, responsible for left-right asymmetry, are similar in structure to respiratory cilia. Embryonic node dysfunction in PCD causes *situs inversus* (termed Kartagener's syndrome) in 50 % of cases (Fig. 4.3a, b) and is associated with congenital heart disease in approximately 6 % of cases [30]. Neonates typically present with respiratory distress of unknown cause and rhinitis. As infants, patients have a persistent wet cough, recurrent respiratory tract infections, rhinitis, and frequently glue ear associated with conductive hearing difficulty. Patients frequently develop sinusitis (Fig. 4.3c). These symptoms may not always be recognised as indicative of PCD and although the mean age of diagnosis is approximately 4 years [31], the range is considerable and reflects local expertise and clinical suspicion. Respiratory symptoms continue into later childhood and adulthood, with many patients developing bronchiectasis, commonly affecting the middle and lower, rather than upper lobes as in CF.

The diagnosis of PCD requires specialist investigation, and a number of different tests should be available, since no one investigation can be considered confirmatory [27, 32].

Extremely low levels of nasal nitric oxide are supportive of the diagnosis of PCD [33]. However, some patients with PCD have been described with normal nitric oxide levels, and levels can be low in other conditions including CF. Nasal nitric oxide measurement should therefore only be used as a screening test, and if clinical suspicion is high, further diagnostic investigation should be conducted even if the levels are normal [21].

Patients should have their respiratory epithelial cells visualised by high speed video microscopy for evidence of ciliary dysfunction (e.g. static, dyskinetic, or vibratory cilia). Subtle abnormalities may be significant, but difficult to recognise; facilities should therefore be based at centres with expertise and a high throughput of PCD diagnostic patients. Following abnormal high speed video microscopy analysis, confirmation of diagnosis by an additional method is required because ciliary dysfunction can be secondary, for example to infection. Most, patients with PCD have diagnostic abnormalities of ciliary ultrastructure on transmission electron microscopy and this used to be considered the 'gold standard' investigation for PCD (Fig. 4.2). However, it is now recognised that at least 15 % of patients with PCD have normal ciliary ultrastructure and this investigation should not be used in isolation. Transmission electron microscopy analysis requires expert interpretation.

Air liquid interface cell culture techniques are particularly helpful where secondary ciliary defects are suspected, for example due to chronic infection. Re-differentiation of basal epithelial cells to ciliated cells is achieved by culturing the cells, allowing a repeat HSV analysis and electron microscopy having reduced environmental factors that compromise

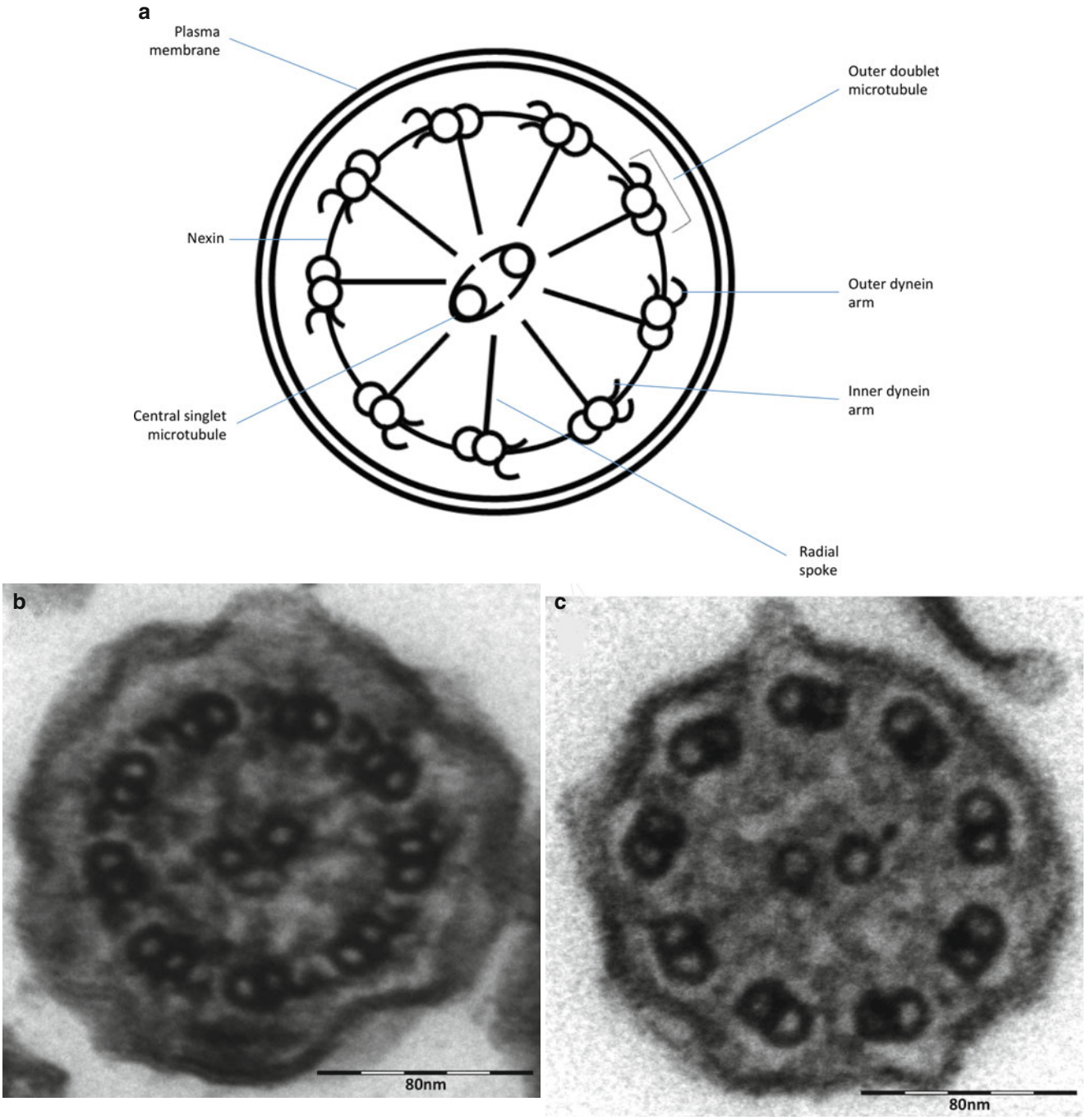

Fig. 4.2 (**a**) Diagram of transverse section of a respiratory cilium as seen by transmission EM. Motile cilia in the respiratory tract and fallopian tubes have a highly organized "9+2" arrangement with nine peripheral microtubule doublets surrounding a central pair of single microtubules running the length of the ciliary axoneme. Nexin and radial spokes maintain the organized structure. Attached to the peripheral microtubules are inner and outer dynein arms. Dynein is a mechanochemical ATPase and generates the force for ciliary beating, hence abnormalities of the dynein arms affect ciliary beating. Transmission EM of a respiratory cilia from (**b**) a healthy individual and patients with PCD due to (**c**) an outer dynein arm defect and (**d**) a radial spoke defect. (**e**) TEM of a sperm demonstrates similar "9+2" ultra-structure (Cartoon image provided by Robert Scott; EM images obtained using FEI Tecnai 12 transmission electron microscope (FEI UK Limited, Cambridge, UK) at 80 kV). Scale bars 580 nm. EM images provided by P. Goggin (Primary Ciliary Dyskinesia Group, University Hospitals Southampton NHS Foundation Trust, Southampton, UK)

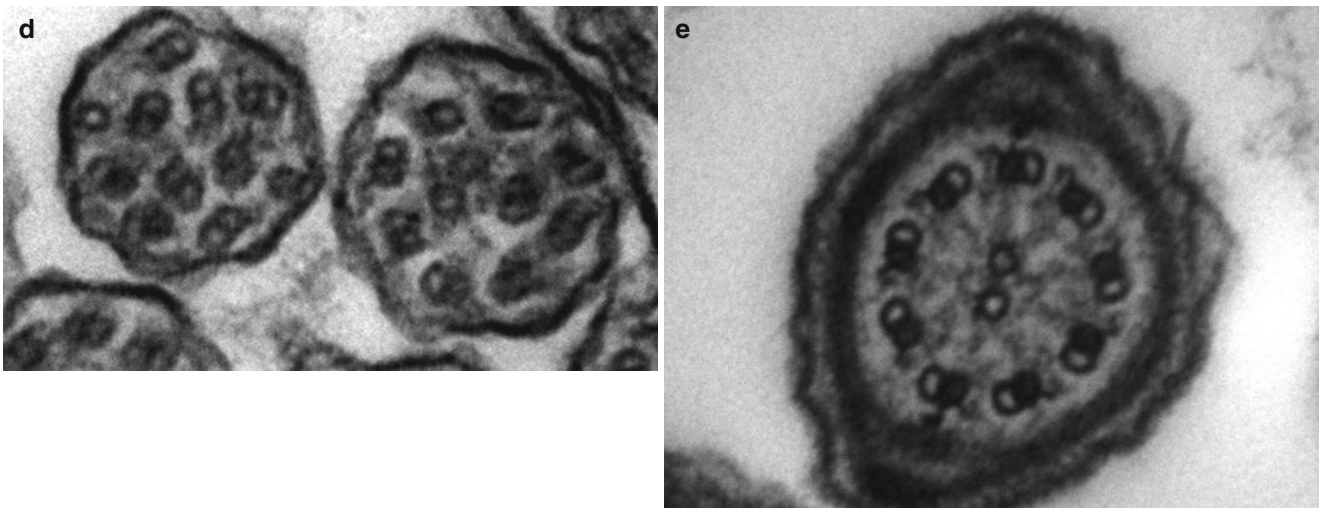

Fig. 4.2 (continued)

ciliary function for example pollution, infection. However, air liquid interface culture is technically demanding and time consuming; it is routinely available in a small number of specialist centres.

Immunofluorescence microscopy analysis, is a promising technique to help in the clinical diagnosis; it is based on the ability to detect and localise intra-ciliary proteins e.g. DNAH5 by immunofluorescence. However, this method is only routinely available at one centre which is based in Germany.

Genetic testing is currently only able to identify perhaps 50 % of PCD cases, but it is an active area of international research with potential for significant advances. Whilst CF is caused by mutations in one gene, PCD is polygenic with over 200 proteins involved in the formation of cilia. Additionally the disease-causing genes are large, making genetic diagnosis of PCD a challenge. Mutations in 24 genes have been associated with PCD to date, mainly encoding for dynein arm components (reviewed in [32, 34], and summarised in Table 4.2). The two commonest mutations, dynein, axonemal, heavy chain 5 (DNAH5) mutation [37] and dynein arm intermediate chain 1 (DNAI1) mutation [35], have a combined prevalence of 17–35 % in patients with PCD and are associated with static cilia on light microscopy, and dynein arm deficiencies on electron microscopy. Other known mutations are all rare. Mutations in the kintoun gene (KTU) [43], which is required for cytoplasmic pre-assembly of axonemal dyneins results in a similar ciliary phenotype to DNAH5. Mutations in the radial spoke head genes RSPH9 and RSPH4A have been reported in PCD patients with abnormalities of the central microtubular pair causing an abnormal rotating movement of the cilia [56]. Patients with mutations in the dynein axonemal heavy chain 11 (DNAH11) have hyperkinetic vibratory cilia, but apparently normal ultrastructure on electron microscopy [39]. There are therefore a variety of ciliary phenotypes seen on microscopy depending on the responsible mutations, but all result in a severe mucociliary clearance impairment, and clinical phenotype is indistinguishable.

In extremely rare cases, PCD has been genetically linked to other ciliopathies. X-linked recessive retinitis pigmentosa, sensory hearing deficits, and PCD have been associated with mutations in the Retinitis Pigmentosa guanosine triphosphatase regulator (RPGR) [63]. A single family has been reported with a novel syndrome that is caused by Oral-facial-digital type 1 syndrome (OFD1) gene mutations characterized by X-linked recessive mental retardation, macrocephaly, and PCD [62].

Young's Syndrome

Young's syndrome, or Barry-Perkins-Young syndrome, is a clinical entity characterised by bronchiectasis, chronic sinusitis and impaired fertility. The diagnosis is considered most commonly in middle aged men presenting with infertility. Although Young's syndrome has been reported in identical twins prompting suggestions of a genetic aetiology, there is some evidence that this syndrome has declined following the removal of mercury from teething powders and worm medicines in the 1950s [64]. Moreover, whilst Young's syndrome and other disorders of mucociliary clearance have partially overlapping symptomatology, a common causative link has not been identified. Indeed the mechanism of reduced fertility in Young's appears to be due to functional obstruction of sperm transport down the epididymal tract rather than due to absence of the vas deferens which is seen in CF or to dysmotility seen in PCD. There are reports that mucociliary clearance is impaired in Young's syndrome [65] but ciliary ultrastructure is largely normal [66]. Similarly, patients with Young's are not frequently carriers of common

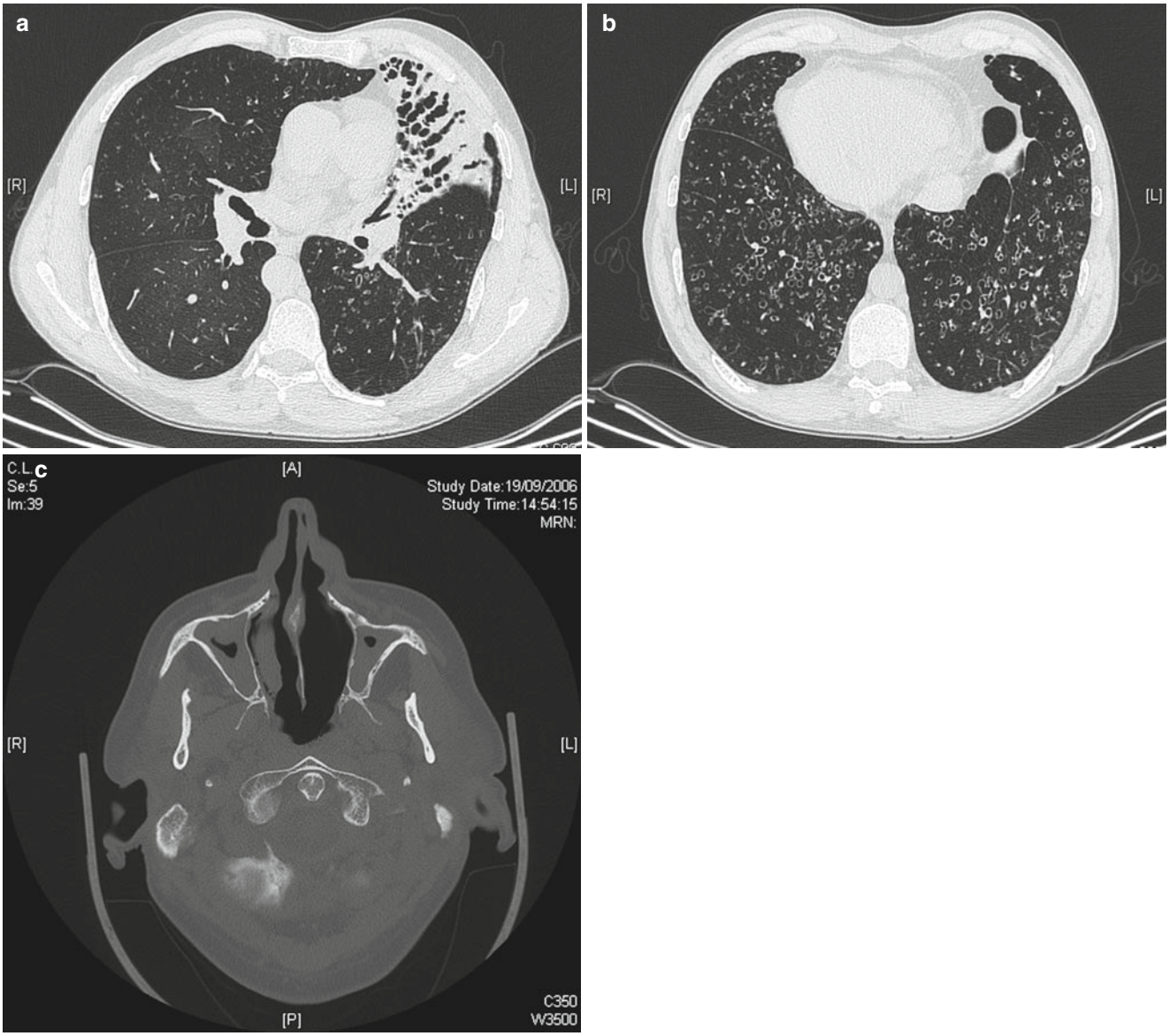

Fig. 4.3 HRCT of the chest in a 49-year old man with primary ciliary dyskinesia and Kartagener syndrome at the time of first evaluation for lung transplantation, demonstrating numerous bronchiectases and consolidation in the anterior lateral segment of the left lower lobe (**a**), and bilateral bronchietasis in the lung bases (associated with centrilobular nodules and tree-in-bud pattern suggestive of bronchiolitis). Note the presence of situs inversus (**b**). Pansinusitis was present in the same patient (**c**) (Courtesy of Pr V. Cottin, University of Lyon, France)

CF mutations [67], although possibly there may be an association with atypical CF mutations [68]. Some authors have even questioned whether Young's syndrome exists as a recognised clinical entity at all [69], and it is quite possible that as diagnoses of rare variants of CF are established, Young's syndrome will disappear as a diagnosis.

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, in the eye and kidney ciliopathies can cause retinitis pigmentosa, autosomal dominant polycystic kidney disease (ADPKD) or nephronophthisis. Primary cilia are similar in structure to the respiratory epithelial cilia (9+2), but in cross section, there is no central pair of microtubules (9+0). There are several case reports of patients with PCD-like disease in association with retinitis pigmentosa [70, 71]. In some patients it may be that both primary and motile cilia are impaired. In others it may be that the problem is purely of primary cilia, with abnormalities of primary

Table 4.2 The genes implicated in PCD

Gene	Ultrastructure defect on electron microscopy	Comments
Genes encoding for outer dynein arm proteins		
dynein axonemal intermediate chain 1 (DNAI1) [35]	ODA defect (± IDA)	2–9 % of all PCD, 4–13 % of PCD with ODA defects [36]
dynein axonemal heavy chain 5 (DNAH5) [37]	ODA defect (± IDA)	15–21 % of all PCD, 27–38 % of PCD with ODA defects [38]
dynein axonemal heavy chain 11 (DNAH11) [39]	Normal	6 % of all PCD [36], 22 % of PCD patients with normal ultrastructure [38]
dynein axonemal intermediate chain 2 (DNAI2) [40]	ODA defect	Rare (<2 % of cases of PCD)
thioredoxin domain containing 3 (TXNDC3) [41]	ODA defect	Rare (<2 %)
DNAL1 [42] encoding the ODA light chain1	ODA	
Genes encoding for assembly, transport or attachment of proteins		
kintoun (KTU)/ dynein, axonemal, assembly factor 2 (DNAAF2) [43]	ODA & IDA defects	12 % of PCD with ODA + IDA defects [36] ktu encodes for a cytoplasmic protein responsible for pre-assembly of dynein arm complexes in the cytoplasm
Leucine rich repeat containing 50 (LRRC50) [44]	ODA & IDA defects	Rare
Dynein, axonemal, assembly factor 3 (DNAAF3) [45]	ODA & IDA defects	
leucine rich repeat containing 6 (LRRC6) [46, 47]	ODA & IDA defects	11 % of PCD with ODA + IDA defects
Coiled-coil domain containing 103 (CCDC103) [48]	IDA and ODA defect	CCDC103 acts as a dynein arm attachment factor. Mutations disrupt assembly of dynein arms
Coiled-coil domain containing 114 (CCDC114) [49–51]	ODA defect	CCDC114 is required for attachment of ODAs in the axoneme. 6 % of PCD with ODA defects [36]
HEAT repeat containing 2 (HEATR2) [52]	ODA absent	HEATR2 localises to cytoplasm suggesting a role in dynein arm transport or assembly
Coiled-coil domain containing 65 (CCDC65) [53]	Normal EM, vibrating cilia	Nexin-dynein regulatory complex component absent from airway cells of patient
ZMYND10 [54, 55]	ODA and IDA absent	Gene is essential for axonemal assembly of dynein arms
Genes encoding for radial spoke head proteins and genes associated with central pair abnormalities		
radial spoke head protein 9 (RSPH9) [56]	Intermittent or complete central pair defect	
RSPH4A [56]		
RSPH1 [57]	Central complex and radial spoke defect	
HYDIN [58]	cilia lack the C2b projection of the central pair apparatus	
Coiled-coil domain-containing protein 39 (CCDC39) [59]	Axonemal disorganisation and IDA defect (sometimes called ‘radial spoke defect’	36–65 % of PCD with IDA defects + axonemal disorganization. CCDC40 is required for the axonemal localization of CCDC39. The mechanisms mediated by these proteins are unclear
CCDC40 [60]	Axonemal disorganisation and IDA defect	24–54 % of PCD with IDA defects + axonemal disorganization [36]
Defect of nexin-dynein regulatory complex		
DRC1 CCDC164 [61]	Axonemal disorganization in small proportion of cilia	Absent nexin-dynein regulatory complex (N-DRC)
Associations with other syndromes		
Oral-facial-digital type 1 (OFD1) [62]	Unknown	One case report
Retinitis Pigmentosa guanosine triphosphatase regulator (RPGR) [63]	Variable	Association with X linked retinitis pigmentosa

pulmonary cilia causing lung disease. This needs further evaluation.

Autosomal dominant polycystic kidney disease (ADPKD) is an example of renal ciliopathy associated with bronchiectasis. It affects between 1 in 400 and 1 in 1,000 people [72]. 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 [73]. A predisposition to bronchiectasis is recognised, although the mechanism for this is not fully understood [74].

Alpha-1 Antitrypsin Deficiency

An association between alpha-1 antitrypsin (AAT) deficiency and emphysema is well-known but there are also reported cases of an association with severe PiZ genotypes and bronchiectasis, 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 and judged this to be clinically significant in 20 [75]. 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 [76].

Disorders of Immunity

Immunodeficiency accounts for a significant proportion of cases of bronchiectasis in developed countries. Recent series suggest as many as 7 % of adults [77] and 20–30 % of paediatric cases in the developed world may be attributable to primary immunodeficiency [1, 10]. Immunodeficiency should be considered following respiratory infections that are unusually severe, recurrent, unresponsive to conventional treatment, or atypical [78]. Common associated features include failure to thrive, severe atopic disease, and occasionally, auto-immune disease [79]. Primary immunodeficiencies include 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 [1, 10]. Disorders of innate immunity are currently poorly characterised but are likely to be responsible for a proportion of cases of bronchiectasis currently labelled 'idiopathic'.

Common Variable Immunodeficiency

Common variable immunodeficiency (CVID) has an estimated prevalence of 1 per 25,000 population and is the commonest immunodeficiency. Presentation is usually in young adulthood but diagnosis may be delayed [80]. Patients affected by CVID display a defective antibody response to protein and polysaccharide antigens and low IgG, IgM and IgA levels. This places affected individuals at risk of recurrent bacterial infection as well as autoimmune disease and malignancy [81]. Clinical features vary in CVID, perhaps reflecting heterogeneity of the molecular defects underlying the disease. Susceptibility loci for CVID have been identified within the MHC class II alleles [82], and polymorphisms in the tumour necrosis factor gene have been also been reported in association with CVID [83]. Mutations associated with CVID have been identified within the inducible costimulator (a molecule expressed by T cells) [84], CD19 (a T cell marker important in B cell development, activation and proliferation) [85], and in transmembrane activator and CAML interactor (a receptor believed to be important in antibody responses to type II T-independent antigens) [86].

In individuals with CVID at least one episode of pneumonia has usually occurred before diagnosis of CVID is made [81]. Possibly as a consequence of delayed diagnosis, the risk of bronchiectasis is greater in patients with CVID than in those with X-linked agammaglobulinemia or other immunodeficiency diseases and may approach 70 % [87]. Bronchiectasis tends to be more common in the lingual, middle and lower lobes. The threshold for HRCT imaging should be low in cases of known or suspected immunodeficiency, particularly if there are signs of persisting lung disease [78].

X-Linked Agammaglobuinemia

X-linked agammaglobuinemia (XLA) is characterised by almost complete absence of circulating B lymphocytes and of all immunoglobulin [88]. Mutations of the Bruton's tyrosine kinase gene cause an incomplete block of B cell development at the pre-B cell stage [89]. This leaves affected patients susceptible to infection by encapsulated bacteria and mycoplasma [90]. More recently 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 [91]. 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 presentation as late as 5 years has been known [92]. Although a recent survey has found less than a third of adults with XLA to be severely affected by bronchiectasis [93], there is evidence

to suggest that the risk of developing significant lung disease increases over time and can be reduced by early detection and treatment [94]. Chronic lung disease, including bronchiectasis, has also been observed in children with IgA deficiency, particularly when associated with IgG2 deficiency [95].

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 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 [96]. 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 [97]. Sufferers are vulnerable to recurrent and severe bacterial and fungal infections, frequently *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 [98]. Most commonly this disorder occurs as a consequence of mutations in the gene encoding for neutrophil elastase [99] but can also be attributable to mutations affecting a mitochondrial protein thought to be involved in protecting myeloid cells from apoptosis [100] or an endosomal protein involved in intracellular signalling [101]. The characteristic feature of this disease is low levels of circulating neutrophils and hence vulnerability to bacterial and fungal pathogens.

Bronchiectasis, alongside severe pneumonias, empyemas and pneumatoceles, is common in children with hyper-IgE or Job's syndrome, in which neutrophil defects occur in combination with a wide variety of lymphocyte and humoral function defects as well as very high levels of serum IgE [102]. Job's syndrome is inherited in an autosomal dominant pattern. Mutation of the signal transducer and activator of transcription 3 or STAT3 gene is known to cause Job's syndrome [103], although in some cases the responsible mutation is unknown. STAT3 is a transcription factor which 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 Job's 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, a rare autosomal recessive disorder characterised by exocrine pancreatic insufficiency, bone marrow dysfunction, leukemia predisposition, and skeletal abnormalities. In most cases, Shwachman-Bodian-Diamond syndrome is associated with mutations in the Shwachman-Bodian-Diamond Syndrome (SBDS) gene located on chromosome 7 [104]. Bone marrow dysfunction results in neutropenia in the majority of patients and may be accompanied by defects in neutrophil mobility, migration, and chemotaxis.

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 cases currently labelled as suffering from 'idiopathic bronchiectasis' will have an underlying cause. Rare instances of bronchiectasis in association with deficiency of C2, or mannose binding lectin, have been reported and an association between deficiency of L-ficolin and bronchiectasis has been reported in adult patients [105]. Complement deficiency is also known to affect the severity of bronchiectatic disease in CVID [106] and in CF [107].

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 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 [108]. The most common humoral immunological defects are diminished or absent serum IgA and IgG2, and impaired antibody responses to vaccines [109]. 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 [110]. Fifty percent of patients die in adolescence from overwhelming bronchopulmonary disease [109].

Collagen Disorders

Although the majority of causes of bronchiectasis are related to defects of mucociliary clearance or immunodeficiency, congenital abnormalities affecting the structure of the bronchial wall can predispose to bronchiectasis. In particular, a number of congenital syndromes of collagen and cartilage abnormalities have been associated with bronchiectasis. This suggests that abnormally compliant or distended bronchi can predispose to bronchiectasis.

Marfan Syndrome

Marfan syndrome is a rare hereditary disorder characterised by skeletal, cardiovascular and ocular abnormalities. Pulmonary abnormalities occur in approximately 10 % of patients, the commonest being spontaneous pneumothorax and emphysema [111]. Although rare, cases of bronchiectasis in adults [112] and children [113] who have Marfan syndrome have been described. Marfan syndrome is autosomal dominantly inherited with variable expression; features of the condition arise as a consequence of a defect in Type 1 collagen. The defect in collagen may be responsible for the reduced tensile strength of the connective tissue leading to bronchiectasis and increased susceptibility to infection.

Other Collagen Disorders

In the 1960s Williams and Campbell first described a series of children with bronchiectasis who had a bronchial cartilage deficiency from the third division with normal trachea and central bronchi [114]. It is hypothesised that the compliant bronchi collapse during coughing, leading to poor airway drainage [115]. The familial pattern and the early onset of symptoms support the possibility that this is a rare congenital syndrome [116]. Williams-Campbell syndrome has most frequently been described in children although adult cases have been reported. CT imaging demonstrates bilateral bronchiectasis affecting segmental and subsegmental bronchi [117]. Cartilage deficiency is not evident outside of the bronchi and the cause of the deficiency is not well understood. It has been hypothesised that children who are born with a bronchial cartilaginous defect develop pathology after suffering a viral respiratory infection in infancy. As a precise genetic defect has not been identified and solitary cases have been reported with greater frequency than familial, the genetic basis of Williams-Campbell syndrome is debateable, indeed secondary cartilaginous damage due to infection and inflammatory change cannot be completely excluded.

A contrasting condition characterised by dilated trachea and large bronchi was first described by Mounier-Kuhn in 1932 [118]. This idiopathic tracheobronchomegaly is associated with varying degrees of bronchiectasis varies in age and severity at presentation but usually presents in mid-adulthood. Males are more frequently affected than females, and a racial predominance has been proposed [119]. The trachea may have a ridged appearance with multiple diverticula. Dynamic collapse of the enlarged airways in expiration, particularly posteriorly, is also likely [120] and pooling of secretions may predispose to lower respiratory tract infections [118]. The aetiology of Mounier-Kuhn syndrome remains uncertain, although histological data suggest that tracheal and bronchial dilatation occur as a consequence of abnormal development of airway connective tissue, with a deficiency of elastic and muscular fibres [121]. Tracheobronchomegaly occurs in association with other congenital connective tissue disorders, including Ehlers Danlos syndrome [122] and cutis laxa [123]. Together with reports of the disorder occurring in siblings [119] this makes an unidentified genetic cause possible, at least in some cases. Generally, there is no curative treatment for the syndrome, although the use of tracheobronchial prostheses may improve symptoms in adults [124].

Other Genetic Predispositions to Bronchiectasis

Bronchiectasis has been reported in association with autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, relapsing polychondritis and inflammatory bowel disease [125]. A genetic association in ulcerative colitis-associated bronchiectasis has recently been reported with functional polymorphisms in the cytokine IFNγ and the neutrophil chemokine, CXCR1 [126]. Yellow nail syndrome is a rare disorder observed in association with a number of systemic diseases including rheumatoid arthritis, and also reported in cases of tuberculosis, immunological disorders and malignancies [127]. This syndrome is characterised clinically by dystrophic yellow nails, lymphoedema and pleural effusion [128]. A significant number of patients also have sinusitis [129], lower respiratory tract infections [130], and bronchiectasis [131]. The syndrome is most often seen in middle-aged individuals although a case report has described bronchiectasis in a 6-year-old [132]. Congenital lymphatic malformation and dysfunction is believed to be responsible for the syndrome [133], although a selective deficiency of humoral immune function has also been suggested [134]. Whilst the exact aetiology is unknown, a genetic component has been proposed [135].

Idiopathic Bronchiectasis

An underlying cause cannot be found in at least 30 % of patients with bronchiectasis, these cases are referred to as idiopathic [1, 10, 14, 77]. Some cases 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 causing 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 [136].

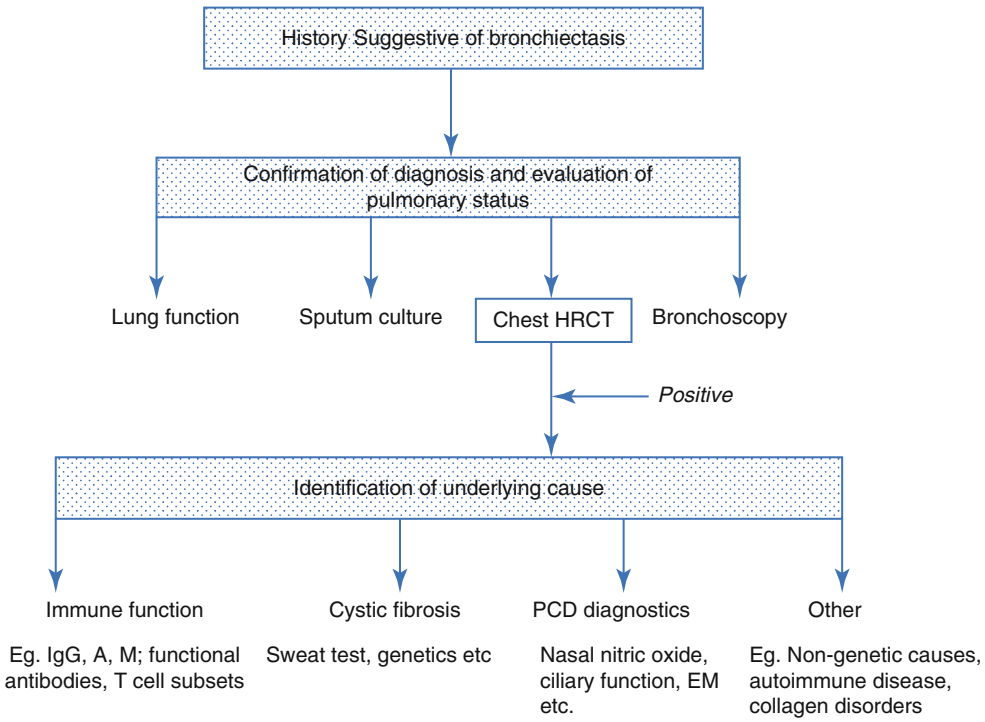

Fig. 4.4 A diagnostic approach to bronchiectasis

Diagnosis

A number of international guidelines exist for the diagnosis and management of bronchiectasis in adults and children [15, 78, 137]. Ideally patients at risk of bronchiectasis should be identified before irreversible damage develops. For example, it is widely accepted that newborn screening for CF, with early introduction of prophylactic treatment, and aggressive management of infections, reduces long-term pulmonary morbidity [138–140]. Similarly in PCD, observational data suggests that lung function decline is stabilised and can even be reversed following diagnosis and instigation of appropriate pulmonary management [141–143].

A diagnostic approach to a patient with symptoms suggestive of bronchiectasis is summarised in Fig. 4.4. HRCT is the gold standard investigation for bronchiectasis, but a number of non-specific investigations assist evaluation of disease severity. A history of recurrent or prolonged wet cough is suggestive of significant endobronchial infection which may progress to bronchiectasis. Individuals in whom bronchiectasis should be suspected include those with a persistent cough for at least 8 weeks [78]. Intermittent hemoptysis is common, particularly in adults. Finger clubbing and persistent wet crackles are indicative of severe disease.

Investigation of patients with prolonged lower respiratory tract symptoms should usually include a standard posterolateral chest x-ray and culture of sputum. Dilated airways with thickened walls are sometimes visible either on chest x-ray as parallel ‘tram tracks’ or ‘ring shadows’. Fluid-filled bronchi may be visible as ‘gloved-finger’ shadows. Situs inversus might direct investigations for PCD (Fig. 4.5). However chest x-ray is not a sensitive test for bronchiectasis, and if the diagnosis is suspected, further investigation is warranted. Patients should have sputum cultured; *Staphylococcus aureus*, *Haemophilus influenzae*,

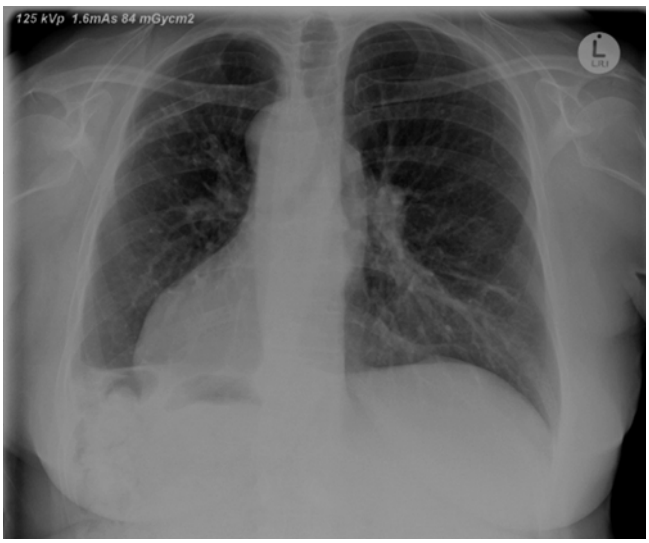

Fig. 4.5 A chest xray of an adult with PCD associated with dextrocardia. There is increased bronchial wall thickening, and also blunting of the right costophrenic angle. The patient had previously had a lung resection via a thoracotomy on the right for bronchiectasis

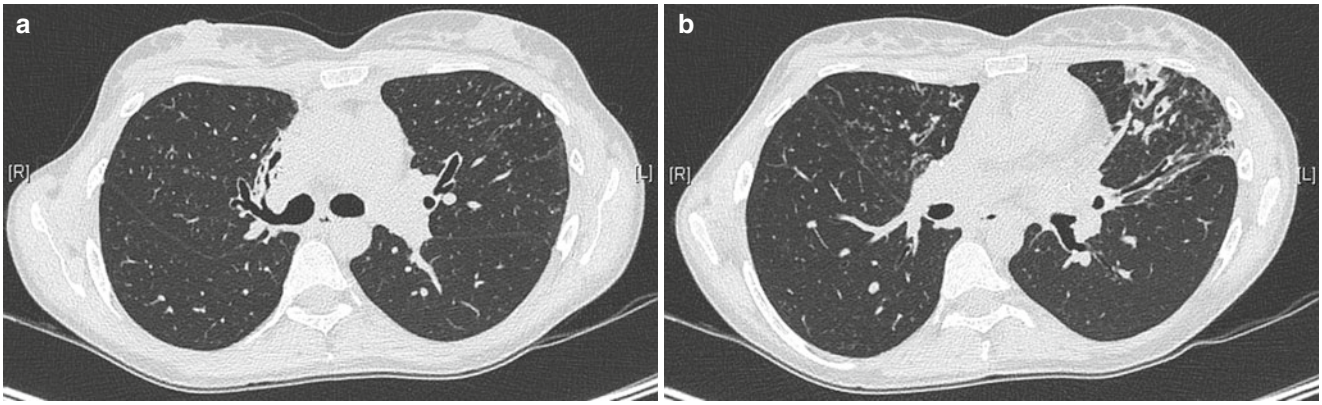

Fig. 4.6 HRCT of the chest in a 32-year old woman with primary ciliary dyskinesia, demonstrating bronchiectasis in the right middle lobe (**a**) and the left upper lobe (**b**). Centrilobular nodules suggest associated bronchiolitis (Courtesy of Pr V. Cottin, University of Lyon, France)

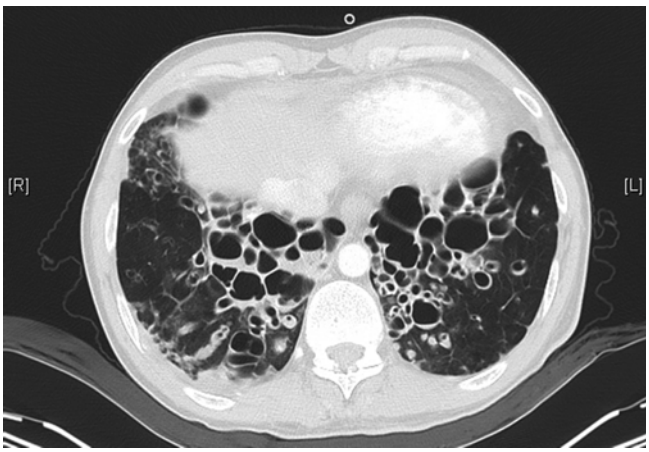

Fig. 4.7 HRCT of the chest in a 47-year old man with primary ciliary dyskinesia evaluated for lung transplantation, demonstrating prominent bilateral bronchiectases in the lower zones of the lungs (Courtesy of Pr V. Cottin, University of Lyon, France)

Pseudomonas aeruginosa, *non-tuberculous mycobacteria or Burkholderia cepacia* are suggestive of significant lower respiratory tract pathology [78]. Measures of lung function are non-specific and non-sensitive in bronchiectasis, but contribute to the assessment of disease severity. Forced expiratory volume in 1 s (FEV_1) is often normal in early disease although a reduced FEV_1 in the presence of normal functional vital capacity (FVC) is common. Standard spirometry is not a good measure of disease decline, and alternative measures are sought. Lung clearance index is a measure that has been suggested to be a good monitor of disease in CF [144] and is being evaluated as an early marker of lung disease in other bronchiectatic diseases such as PCD [145].

High-resolution computed tomography (HRCT) has sensitivity and specificity in excess of 90 % [146] and may detect signs of bronchiectasis not identified by plain film imaging [147]. For this reason HRCT is the gold standard diagnostic investigation (Figs. 4.6a, b and 4.7). Diagnostic radiological criteria were described by Naidich et al. in 1982 [148] and are also summarised in the Fleischner Society: glossary of terms for thoracic imaging [149]. Characteristically enlarged bronchi seen in cross-section are larger than the accompanying arteries giving rise to the 'signet ring' sign. Other characteristic features include dilated airways with air-fluid levels that do not taper and remain visible in the extreme lung periphery [150]. Expiratory HRCT images can be useful. Parenchymal hypoattenuation may identify small airways disease due to air-trapping associated with mucous-filled bronchi in bronchiectasis and evidence of bronchial wall or tracheal collapse can also be detected, providing an alternative investigation to bronchoscopy [151]. 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 [152].

Fibreoptic bronchoscopy should be considered in patients with a prolonged wet cough to assess airway structure and calibre and exclude pathology such as severe tracheomalacia, bronchomalacia or tracheal bronchi which may contribute to bronchiectatic change. 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, investigation of the underlying cause should be sought. The clinical history should direct investigations which will usually include investigation for CF, PCD and immunodeficiency (Table 4.3).

Table 4.3 Characteristic features and diagnostic criteria for bronchiectasis of known genetic origin

Diagnosis	Genetic basis	Suggestive symptoms	Age at diagnosis	Diagnostic criteria
Cystic fibrosis	Mutation of CFTR gene 7q31-7q32	Meconium ileus	Birth if discovered by screening, otherwise presentation is generally in infancy due to failure to thrive or recurrent respiratory infection. Approximately 10 % of cases present as adults.	Immunoreactive trypsin newborn screening
	Most commonly the ΔF508 mutation	Rectal prolapse		Sweat chloride testing
		Failure to thrive		Genotype analysis
		Steatorrhea		CF Trust guidelines [153]
		Nasal polyps		
		Chronic sinusitis		
		Male infertility		
Primary ciliary dyskinesia	Polygenic disorder affecting cilial structural proteins [32]	Neonatal tachypnoea	Although symptoms may be present in the neonatal period these are often identified retrospectively. Diagnosis can be at any stage of life although mean age of diagnosis in childhood is 4 years, and many adults remain undiagnosed.	Ciliary biopsy for high speed video microscopy, transmission electron microscopy and air liquid interface cell culture techniques
		Chronic otitis media with possible speech delay		Nasal nitric oxide measurement
		Chronic rhinitis		Consensus guidelines [39, 154]
		Situs inversus		
Common variable immunodeficiency	Mutations in but not limited to ICOS, TNFRSF13B, TNFRSF13C and CD19 genes	Low immunoglobulin levels	Median age of symptom onset is third decade although may be earlier. Diagnosis is often delayed by 5–10 years from symptom onset.	IgG and IgA and/or IgM
		Recurrent bacterial infections		>2 SD below mean for age
				Defective antibody response to protein and polysaccharide antigens
				Diagnostic criteria [155]
X-linked agammaglobulinaemia	Mutation of Bruton's tyrosine kinase gene	Male patient	Prenatal diagnosis possible in families where mutation is known. Presentation generally in the first year of life although can be up to 5 years	IgG and IgA and IgM > 2 SD below mean for age
		Onset beyond the first 6 months of life		Absent isohaemagglutinins and/or poor response to vaccines
		Low immunoglobulins and absent circulating B cells		Diagnostic criteria [155]
		Encapsulated bacteria and mycoplasma infections		
Chronic granulomatous disease	Mutations affecting NADPH oxidase	Recurrent bacterial and fungal infections	Presentation at mean age of 5 years for x-linked forms and 10 years for autosomal recessively inherited disease	Abnormal nitro blue tetrazolinium reduction Respiratory burst <5 % of control in activated neutrophils
	gp91, p22, p47, p67 phox	Liver, perirectal, lung or bone infection		Diagnostic criteria [155]
		Failure to thrive		
		Hepatosplenomegaly lymphadenopathy		
Marfan syndrome	FBN1 mutations in fibrillin gene on chromosome 15	Ectopia lentis (displacement of the lens of the eye)	Bronchiectasis rare but case reports in both paediatric and adult patients.	Clinical diagnosis based upon family history, aortic root dimensions and 'Ghent' scoring of systemic features [156]
		Aortic dilatation		
		Distinctive body habitus		
		Spontaneous pneumothorax		

Treatment

The overall aims of management should be to treat inflammation and to maximise lung function, exercise tolerance, quality of life and nutrition [78]. In children, it is estimated that identification of a specific cause of bronchiectasis prompts a management change in over 50 % of cases [157]. Identification and prompt treatment of any underlying cause is an important treatment aim as it can significantly limit lung damage and improve prognosis [157]. Treatment is directed at reducing exacerbation frequency as this has a positive impact upon quality of life and may prevent disease progression [158]. Treatment includes promoting clearance of secretions and use of antibiotic therapies both to prevent and to treat recurrent infection. In addition to routine vaccination schedules, patients should receive pneumococcal and influenza vaccinations and avoid exposure to tobacco smoke. It is also important to achieve and maintain an adequate nutritional status in order to support immune function and tissue repair; iron deficiency, in particular, should be avoided as it is known to increase the risk of pneumonia. Treatment is best delivered within a multidisciplinary team where specialist medical, nursing, pharmacy and dietetic expertise can be maintained and promoted. Input from genetic counsellors may be particularly helpful around the time of diagnosis and when planning future children.

Many management strategies focus upon common mechanisms underlying bronchiectatic disease, however, these strategies are often based upon an extrapolation of treatments proven to be effective in the more common disorders such as CF and may not be appropriate for other forms of diffuse bronchiectasis of genetic origin. Specific randomised controlled trials are required, which by necessity for rare diseases will be multi centre and likely require international collaboration. Underlying pathophysiology is different between diseases and optimal treatment is therefore likely to differ; appropriate outcome measures are similarly likely to differ.

Airway Clearance

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 airway oscillation devices. The aims of physiotherapy include mobilising and aiding clearance of secretions, and maximising ventilation efficiency and exercise tolerance. Although physiotherapy is of proven benefit in CF [159] there are few studies demonstrating the efficacy of physiotherapy in non-CF paediatric bronchiectasis that can guide frequency or choice of therapy. Generally it is believed that all patients should be taught a suitable airway clearance technique for use during exacerbations and those patients with a chronic productive cough should be encouraged to conduct regular chest physiotherapy [78].

The most commonly used airway clearance technique, 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. CT scanning can help to identify affected bronchopulmonary segments so that appropriate postural drainage positions can be selected. Postural drainage positions for the mid and basal zones of the lung require a head-down tilt which may be uncomfortable for the breathless patient; modified horizontal positions for postural drainage and the use of non-invasive ventilation during tilt manoeuvres have been suggested as potential solutions to this problem. Positive end expiratory pressure (PEP) techniques provide an alternative to physiotherapy based upon the active cycle of breathing techniques; there is evidence that oscillating PEP devices, such as a Flutter valve or Acapella, when combined with postural drainage and the forced expiration technique are equally as efficacious in terms of sputum clearance as a combination of active cycle of breathing and postural drainage [160]. A further alternative 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. Whilst autogenic drainage has been demonstrated to be superior to no physiotherapy it is unclear how this technique compares to others in terms of objective outcomes such as sputum clearance or airway resistance [161]. Given the absence of a clear superiority of any one technique, patient acceptability is an important determinant of the techniques employed, the Flutter, for example, often being preferred over active cycle of breathing by patients who perceive it to be less time-consuming [160].

In CF, airway clearance during physiotherapy may be improved by use of humidification or inhaled hyperosmolar agents such as hypertonic saline or mannitol prior to treatment. Hypertonic saline is thought to induce liquid flux from the epithelium into the mucus layer, altering its rheology such that it is cleared more easily. Hypertonic saline should be used with caution in patients with significant reactive airways disease because of the potential for bronchoconstriction. Treatment with hypertonic saline, however, has been shown to improve secretion clearance above that achieved by either nebulised saline, nebulised terbutaline or a combination of both treatments in individuals with stable non-CF bronchiectasis [162]. In contrast, the benefit associated with aerosolised recombinant DNase treatment in non-CF bronchiectasis appears to be limited, possibly because there are fewer airway neutrophils in non-CF bronchiectasis.

Nebulised DNase is therefore not generally recommended [78, 163], although anecdotal accounts of successful DNase treatment of PCD patients have been reported [164, 165].

Bronchodilators are likely to be of greatest benefit when bronchial hyperreactivity is demonstrable. There is some evidence that bronchodilator therapy may improve ciliary beat frequency and thereby aid airway clearance [166, 167], but no randomised controlled studies have demonstrated a therapeutic effect in either paediatric or adult bronchiectasis [168–171].

There is little research on the effects of physical exercise in patients with bronchiectasis and less still on those with non-CF bronchiectasis. Data from a limited number of studies suggest that exercise training has a positive effect on exercise capacity, strength and lung function in patients with CF [172], and that pulmonary rehabilitation and inspiratory muscle training may improve endurance and health-related quality of life [173]. It is not, however, possible to make recommendations regarding the particular type of exercise most likely to be beneficial. In the authors' experience exercise that the patient enjoys is beneficial in maintaining lung health and improving quality of life.

Management of Infections

Antibiotic therapy may be used continuously as prophylaxis or intermittently in response to exacerbations. In infants with cystic fibrosis diagnosed following newborn screening, prophylactic flucloxacillin treatment has been shown to reduce cough and hospital admission in the first 2 years of life [174]. In adults with non-CF bronchiectasis long-term high dose oral amoxicillin has been shown to reduce airway inflammation [175] and long-term macrolide treatment, for example with azithromycin, has also been suggested to be a beneficial approach [176]. Macrolides have additional effects beyond their anti-bacterial actions which may be useful in the context of bronchiectasis. Macrolide therapy can reduce inflammatory cytokine release [177] and neutrophil influx and are also believed to reduce biofilms. [178] There is evidence that long-term prophylactic antibiotic therapy is effective in reducing sputum volume and exacerbation frequency [179, 180]. There is a concern that long-term use of antibiotics may accelerate the development of antibiotic resistance, particularly in the case of long-term quinolone prophylaxis for patients colonised with Pseudomonas [181]; regular testing of sputum for culture and sensitivity is essential. In patients chronically colonised with *Pseudomonas aeruginosa* nebulised colistin may improve quality of life and slow the rate of lung function decline [182].

Antibiotic choice should reflect the fact that *Streptococcus pneumoniae*, *Moraxella catarrhalis* and non-encapsulated *Haemophilus influenzae* account for the majority of positive isolates but treatment choice should be individualised based upon the patient's history of infection. Persistent pseudomonas infection is less common in children the United Kingdom and Europe [10] than in adult patients with non-CF bronchiectasis. Inhaled tobramycin has been demonstrated to reduce *Pseudomonas aeruginosa* load in sputum [183]. In patients with immunodeficiency, antibiotic therapy needs to reflect the pathogens to which a particular disease confers vulnerability [184]. Co-trimoxazole and itraconazole prophylaxis are required in CGD, for example.

Antibiotics are recommended for exacerbations that present with an acute deterioration with worsening cough or increased sputum volume or purulence over several days [78]. there are no randomised placebo-controlled trials of antibiotic use in infective exacerbations of bronchiectasis. During exacerbations, antibiotic choice is usually empirical; initially, selection should be based upon local microbial patterns, sensitivities and cost. Previous culture results may also inform antibiotic choice, although if there is no previous bacteriology amoxicillin is a reasonable first choice [78, 185]. High dosages for relatively prolonged periods may be necessary to achieve bactericidal antibiotic levels in the endobronchial mucus [186]. Generally a 14 day course is recommended. Before starting antibiotics a sputum sample should be sent for culture and antibiotic prescription modified depending upon the result. However, 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 bronchoalveolar lavage specimens may be required. Antibiotic cover may be needed even during viral exacerbations to prevent an increase in bacterial load as a consequence of the reduced lysozyme release and bactericidal activity associated with such exacerbations [187].

Anti-inflammatory Management

Inhaled corticosteroids have been employed with the aim of reducing inflammatory damage in the lung and systemic corticosteroids may be used to treat acute exacerbations of reactive airways disease. Randomised controlled trials in adult patients with bronchiectasis have shown extremely high dose inhaled corticosteroids to improve FEV_1 but not symptoms or exacerbation frequency; no studies have been conducted in children and corticosteroids are not routinely recommended in bronchiectasis uncomplicated by asthma [78, 188].

Other unproven medical therapies of possible benefit include and leukotriene-receptor antagonists, due to their bronchodilator and anti-inflammatory properties; indomethacin, which may reduce sputum elastase [189] by blocking the cyclooxygenase pathway; and methylxanthines, which are believed to have anti-inflammatory properties and may

increase respiratory muscle efficiency even at doses too low for a bronchodilator effect.

Immune Therapy

Patients with CVID benefit from immunoglobulin substitution therapy; this has been proven by a randomised multicentre trial conducted in the Netherlands [190]. Subcutaneous infusions are better tolerated by patients than intravenous infusion and may achieve more stable trough levels with a lower risk of adverse reactions [191]. Doses may need to be increased in the presence of active lung disease as this increases immunoglobulin turnover [192]. Subcutaneous immunoglobulin infusion has been demonstrated to reduce the frequency of exacerbations and to slow bronchiectasis progression. Efforts to reconstitute the immune system can also be effective. Recombinant IFNγ therapy, for example, is also effective in reducing the number of severe infections [193, 194] and recombinant granulocyte stimulating factor can be used in severe congenital neutropenia [195].

Surgery

Surgical treatments were used more widely prior to the introduction of effective antibiotic therapy [12]. There remains a place for surgical treatment, particularly pulmonary segmental resection when damage is severe but well localised. In such cases it is useful to demonstrate pre-operatively the extent and exact site of any defect in ventilation or perfusion to the affected portion of the lung [196]. Mortality and morbidity associated with early surgical procedures were high but the introduction of effective antibiotic treatment and improvements in surgical techniques have dramatically reduced perioperative risks. Surgery has the advantage of removing infected tissue and thereby preventing spread of disease to other areas of the lung and, in some instances, may be curative [197]. Overall mortality ranges from 0 to 3.5 %, whilst the most common complications of lung resection are atelectasis, bronchopleural fistula, empyema and wound infection [198]. End-stage diffuse bronchiectasis may be treated with bilateral lung transplantation; this is mainly limited to patients with CF. A study of 78 PCD patients from the US reported very severe disease with lung failure in 38 % of adults. All of these severely affected individuals had received a lung transplant, were awaiting one, or were oxygen dependent [199]. Outcomes can be improved by pre-operative nutritional supplementation and aggressive antimicrobial therapy tailored to likely colonising organisms. In appropriately selected patients transplantation has been shown to improve quality of life and to prolong survival [200, 201].

Potential Future Therapies – Gene Therapy

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 [202, 203]. 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. This type of therapy is limited to correction of genetic defects in either terminally differentiated, long-lived post-mitotic cells or easily accessible stem cells. To treat stem cells such as those of the haematopoietic system, implicated in primary immunodeficiency, a viral vector capable of integration within the host genome is required for gene delivery. Barriers to the success of this treatment strategy are: (1) low protein expression due to poor gene transfer [204], (2) risk of insertional mutagenesis [205], and (3) immunogenicity of the vector or transgene product [206]. Nevertheless gene-modified autologous bone marrow transplantation represents a promising treatment free from the immunological complications associated with transplantation from a HLA-mismatched donor. Whilst bone marrow transplantation from an HLA-matched sibling donor confers an approximately 80 % cure of primary immunodeficiency and that from a fully HLA-matched unrelated donations confer a 70 % chance of cure, survival following an HLA-mismatched donation is substantially less (37 %) and complicated by graft-versus-host disease, partial immunological reconstitution and attendant infection risk [207].

It appears that in order to replenish the peripheral pool of immune cells with cells containing the transduced gene, the transduced cells should have a selective advantage. The importance of selective advantage is seen in gene therapy of adenosine deaminase deficiency (a primary immunodeficiency associated with pneumocystis and CMV infection leading to interstitial and alveolar infiltrates, although not commonly bronchiectasis). T lymphocyte precursors genetically modified to contain the adenosine deaminase enzyme missing in this disorder are able to metabolise toxic purine products and have a selective advantage over unmodified lymphocytes; the success of the gene-transfer is reduced by treatment with adenosine deaminase enzyme replacement therapy as this reduces the selective advantage of the modified cells [208]. Similarly rare spontaneous partial phenotypic correction of severe T cell immunodeficiencies have 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 [209]. 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 treat-

ment prior to gene-therapy which leads to a higher proportion of transduced progenitor cells due to better engraftment.

Preliminary but promising results for gene therapy have been reported following non-myeloablative conditioning with busulfan and gene-therapy treatment in two adults with X-linked CGD [210]. A retroviral vector containing wild-type gp91^{phox} was used and following transplantation of genetically modified autologous CD34^{+} cells 10–15 % engraftment of transduced granulocytes was achieved and there was notable clinical improvement in both patients. Clonal expansion of myeloid cells, thought to be due to retroviral vector insertions near cellular proto-oncogenes, complicated this therapy although malignant transformation was not observed during follow-up.

Clinical 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 glue ear but there is otherwise no family history of note.

Using HSV 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. 4.8) with 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 [29].

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 which 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 case:

- PCD often presents in the neonatal period but diagnosis is often delayed until later childhood [22].
- Diagnostic evaluation is often complicated and requires specialist expertise.
- 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.
- The case patient is under specialist PCD care. However, as with most orphan diseases, the majority of patients are managed by non-specialists. Inappropriate respiratory treatment is more likely to lead to bronchiectasis and a poorer prognosis. Inappropriate ENT care can lead to poor management of hearing impairment and rhino-sinus disease.
- Unlike many orphan diseases, consensus statements are available to provide guidelines for diagnosis and management of PCD [39, 154]. However there have been no clinical trials in PCD and management guidelines are extrapolated from more prevalent diseases; this is almost certainly inappropriate.
- The management of hearing impairment caused by glue ear is controversial in PCD (reviewed in [21]) but many PCD specialists report excess complications caused by grommets (for example otorrhea and failure for hearing to improve) and recommend that patients with PCD should be treated with hearing aids as the primary approach.

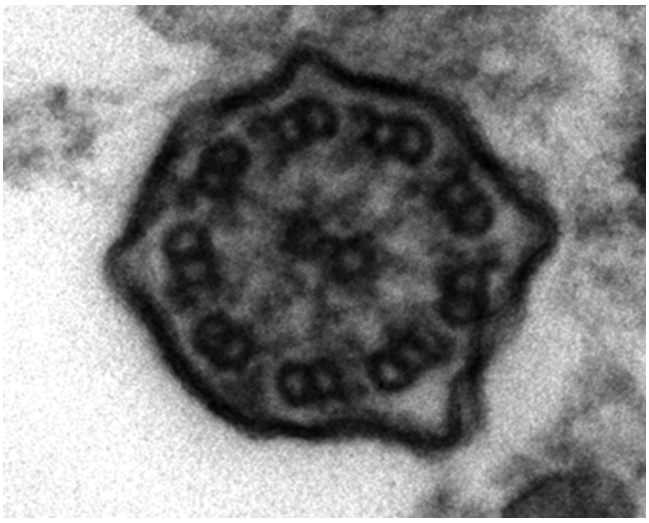

Fig. 4.8 TEM of a cilium from the patient described in the Vignette. Despite having PCD, the patient has normal ciliary ultrastructure by EM. EM images obtained using FEI Tecnai 12 transmission electron microscope (FEI UK Limited, Cambridge, UK at 80 kV). Scale bars 580 m. EM images provided by P. Goggin (Primary Ciliary Dyskinesia Group, University Hospitals Southampton NHS Foundation Trust, Southampton, UK)

Summary

It is likely that the true incidence of bronchiectasis with a genetic basis is underestimated. As our understanding of innate immunity and ion-transport disorders are better characterised, a number of cases currently labeled as 'idiopathic' will have their aetiology elucidated. As with other Orphan Diseases, the diagnosis and management of patients with bronchiectasis is largely determined by local interests and provision, and many patients find it difficult to access appropriate care. Most doctors have little experience of rarer causes of bronchiectasis and will base management on evidence from CF. Indeed, the evidence base for managing non-CF bronchiectasis is poor. For example there have been no clinical trials in PCD, which is distinctly different from CF in underlying pathophysiology, and is likely to benefit from different management. The CF community has made substantial advances in recent decades, resulting in improved morbidity and mortality. These advances have been beneficial to the care of patients with non-CF bronchiectasis, but more rapid developments are likely if clinical standards and evidence based guidelines are individualized for different diseases.

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Allergic Bronchopulmonary Mycosis

5

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Introduction and Epidemiology of Allergic Bronchopulmonary Mycosis

Aspergillus fumigatus (AF) is a ubiquitous mould, the most commonly responsible for allergic bronchopulmonary aspergillosis, referred to as ABPA. Other *Aspergillus* species (*Aspergillus niger*, *A. terreus*, *A. ochraceus*, *A. orizae*, *etc.*…), have been identified in ABPA, sometimes after occupational exposure (i.e.: *A. orizae* in small-scale soy sauce makers) [1]. Other fungi have been exceptionally associated with allergic bronchopulmonary mycosis: *Candida spp.*, *Penicillium spp.*, *Torulopsis spp.*, *Fusarium spp.*, *Geotrichum candidum*, *Stemphylium lanuginosum*, *Culvularia lunata*, and *Drechsleria hawaïensis*, *Helminthosporium Spp*, *etc.*… [2–4]. Evaluation of clinical differences between ABPA and other allergic bronchopulmonary mycosis are difficult because criterias leading to allergic bronchopulmonary mycosis diagnosis are often incomplete (cases described without asthma, lack of precipitins…) and most descriptions are case reports. Recently, *Schizophyllum commune* as the aetiological agent of allergic broncho-pulmonary mycosis (ABPM) and pulmonary fungal ball has been reported in Japan and in North America [5]. ABPM related to *Schizophyllum commune* presented with and without asthmatic conditions and responded to corticosteroids associated or not with itraconazole [5].

ABPA was described by Hinson [6] in 12 asthmatics with recurrent pulmonary infiltrates, blood and sputum eosinophilia, and *Aspergillus* hyphae in their sputum. Pepys identified precipitating antibodies to AF in 1969 [7]. ABPA occurs in atopic patients with asthma or in cystic fibrosis (CF), (rare before the age of 6), both diseases characterised by an activated/injured bronchial epithelium. In asthma as in CF, there is evidence that the barrier function of the airways epithelium is impaired and that epithelial cells product more inflammatory and fibrotic mediators compared with normals [8–10]. CF is the main, if not exclusive, underlying disease in childhood. ABPA occurs in genetically predisposed patients, having atopy and in part some epithelial dysfunction. Respiratory epithelial cells have a key role. They act as a barrier to invasion by inhaled AF species, promote mucociliary clearance and have the ability to ingest AF conidia. Dendritic cells located among epithelial cells sense AF motifs via pathogen-recognition receptors, and prime T-cell response, through a large predominant Th2 response in ABPA. Persistence of AF in the airways and/or inadequate response to AF leads to the development of bronchial inflammation and a hypersensitive response.

Prevalence of ABPA in asthma and CF varied according to regions. It is well defined in CF registers: 0.9 % in the south-west of the USA to 4 % in the west [11], and 7.8 % in Europe, ranging from 2.1 % in Sweden to 13.6 % in Belgium [12]. In asthma, ABPA affects 1–2 % of asthmatics [13], but recent data showed a prevalence of 12.9 % ranging from

We have a very special thought for the memory of Dr Isabelle Tillie-Leblond, who passed away soon after completing her chapter.

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Table 5.1 Classification of diseases induced by *Aspergillus fumigatus*

Infectious diseases	Invasive aspergillosis
	Chronic necrotising pulmonary aspergillosis/Aspergilloma
Hypersensitivity diseases	Aspergillus sensitisation in asthma
	And severe asthma associated with fungal sensitization (SAFS)
	Hypersensitivity pneumonitis
	Allergic bronchopulmonary aspergillosis

2 to 32 % in asthmatics [4, 14]. The prevalence is dependent on the populations studied, the severity of asthmatic patients recruited and geographical disparities that may explain these differences. Nevertheless, the prevalence in a broad population of unselected patients with asthma is not known. Family occurrence of ABPA is rare but described [15]. ABPA have been described with previous tuberculosis [16, 17], and under infliximab for sarcoidosis [18].

The various pulmonary manifestations related to AF are complex, mainly dependent on the status of host defence. AF is responsible for infections and hypersensitivity diseases (Table 5.1). It may be saprophyte in airways. Special attention and a critical approach are necessary when cases of ABPA have been described in COPD patients (with co-morbidities: alcohol, systemic corticosteroid, diabetes) or congenital immuno-deficiencies (congenital chronic granulomatous disease, hyper-IgE syndrome, etc.…) [19, 20]. In these cases, local or systemic host-immune responses are altered (mainly phagocytic impairment) and may be responsible for chronic necrotising pulmonary aspergillosis and invasive aspergillosis. This is well illustrated in chronic granulomatous disease characterized by an inherited disorder in nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [21]. In these cases, invasive aspergillosis is a main cause of death [21]. Erroneous diagnosis of ABPA leading to the prescription of corticosteroids could be dangerous as it will enhance AF growth [22–25].

Aspergillus: An Ubiquitous Fungus

Aspergillus organisms are filamentous fungi and are extremely resilient. AF is ubiquitous in the environment, in water, soil spaces, wood chips, grass mowings, potted plants, indoor air, walls and ceilings, building demolitions, etc… The spores are capable of withstanding extreme atmospheric conditions, grow at temperatures ranging from 15 to 50 °C and survive even at >55 °C [9, 26]. Inhalation of spores (conidia) from the environment is followed by growth of hyphae in the mucus of the bronchial tree. AF germination is the transformation from conidia to hyphae. In its mycelium phase, AF consists of 7–10 μm long, uniform, septate hyphae with dichotomus branching at an angle of 45°. The hyphae can be identified using the PAS and Grocott's stains. Reproduction is characterised by the formation of conidiophores with terminal vesicles producing chains of spores. The spores measure 2–4 mm in diameter. AF grows on Sabouraud dextrose agar slants [27]. It takes about 12 h for AF to germinate at 37 °C on simple media and 4–5 h on rich media. Conidiophores and spores may be seen together, mainly in structures that are in contact with the atmosphere.

The relationship between ABPA development and level of AF exposure remains unclear, even if high levels of AF exposure have been associated with ABPA exacerbation and if the prevalence of ABPA varies according to climate [28].

Pathogenesis: From AF Spore Inhalation to ABPA

Factors underlying the development of ABPA remain unclear. Up to 25 % of asthmatics are sensitised to AF [29] and multiple sensitisations to fungi should be associated with more severe asthma [30]. Yet, few asthmatics develop an ABPA. ABPA mainly occurs in atopic patients. The bronchopulmonary response to inhalation of *Aspergillus* spores involves three associated factors: fungal proliferation, hypersensitivity and abnormalities of the bronchial epithelium (Fig. 5.1). After *A. fumigatus* spores are inhaled into the bronchial airways, they are usually trapped by the luminal mucus and then destroyed by mechanisms of local defence. However, proliferation of *A. fumigatus* with mycelia formation can occur if there are abnormalities in the immune response (local defence with development of an aspergilloma inside a residual cavity devoid of alveolar macrophages and neutrophils, or in COPD patients; systemic defence in cases of invasive aspergillosis). The second response mechanism is hypersensitivity likely to induce either an IgG response with complement activation (rare cases of hypersensitivity pneumonitis) or, in atopic patients, an IgE response consecutive to sensitisation to *A. fumigatus* (allergic asthma). ABPA is different and is characterised by markedly elevated *Aspergillus*-specific IgE, IgA and total IgE antibodies, eosinophilic pulmonary infiltrates, bronchiectasis and fibrosis. Several associated concomitant factors favour ABPA development. Among these factors, the respective roles of genetics and pre-activation of epithelial cells (and the extent to which this activation facilitates bronchial penetration of the fungus) as well as the immune response (bronchial/bronchiolar inflammation, remodelling and bronchial destruction) are not yet fully

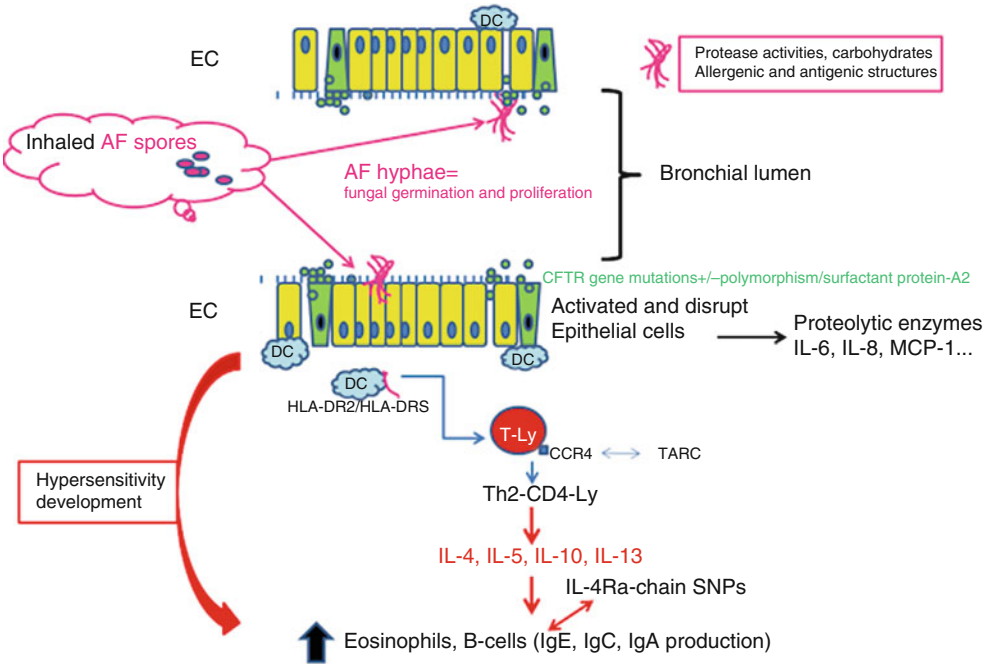

Fig. 5.1 Pathophysiology of ABPA. AF spores germinate in a predisposing environment. AF products (hyphae++) disrupt epithelial junctions and activate epithelial cells (EC)-secreting proteolytic factors and pro-inflammatory mediators. Genetic factors (implicated in surfactant production, CFTR gene) may limit the host defence and encourage AF germination. Allergens are presented by the dendritic cells (DC)/macrophages (which preferentially express HLA-DR2 and 5) to T lymphocytes, with a predominant Th2 response. IL4Ra chain SNPs in ABPA may in part induce an IL-4 "hypersensitivity". This results in the production of high levels of IgE and IgG

understood. Indeed, mechanisms involved in ABPA development are complex (Fig. 5.1). Pepys suggested that ABPA was the result of type I and type III immunologic responses, classified according to Gell and Coombs. However, this classification probably provides an excessively restricted view of ABPA pathogenesis.

A Main Role for Genetic Factors

CD4 + Th2 lymphocytes from ABPA patients are restricted to six MHC class II human leucocyte antigen (HLA)-DR subtypes. Genetic studies suggest that **HLA-DR2 and HLA-DR5** are associated with susceptibility to ABPA, whereas HLA-DQ2 is associated with resistance [31–33]. Restricted genotypes within these HLA subtypes also influence the risk of ABPA. Chauhan et al. [31] has created an interesting hypothesis. He has shown that the affinity of Aspf1 for HLA-DR is low and that it may favour a Th2 cell response [31]. Indeed, T-cell receptor (TCR)-mediated signalling pathways can be modified by stimulating T cells using peptides with low affinity for a particular TCR [34]. It has been demonstrated in several model systems, *in vivo* and *in vitro*, that providing a weak TCR-mediated signal can preferentially generate IL-4-producing cells and Th2 differentiation. A strong HLA-DR-AgTCR affinity may tend to favour a Th1 cellular response, whereas low affinity favours a Th2 humoral response [35–37].

The combination of these data with mutations of the cystic fibrosis trans-membrane conductor regulator (**CFTR**) gene might determine the outcome of ABPA in patients with CF, but also in some asthmatics [38]. Marchand et al. found that the frequency of (CFTR) gene mutations was higher in non-CF patients with ABPA compared with allergic asthma, even though both groups showed normal sweat chloride concentrations [39]. Similar conclusions were made by Miller et al. [40]. This indicates that CFTR gene mutations are likely to participate in the development of ABPA, even if there are no data concerning the quality of mucus in these cases.

AF conidia bind surfactants A and D. Surfactant enhances phagocytosis of AF. Saxena et al. identified an association between two polymorphisms in the collagen region of pulmonary **surfactant protein-A2** (ala91pro, arg94arg) and a predisposition to ABPA and severity of the disease [41]. About 80 % of patients carrying both alleles had ABPA, while 50 and 60 % carrying each allele had ABPA ($p = 0.0079$; OR: 10.4) [41].

Familial occurrence of ABPA is described, in parent-child but also in siblings [15, 42]. It represents 5 % among a population of 164 patients with ABPA [15].

A. fumigatus Mediators and/or Antigens: Actors of the Local Pro-inflammatory Response and the Specific Immune Response

A. fumigatus antigens have the capacity to interact with epithelial cells of the bronchial mucosa by releasing proteolytic enzymes that cause epithelial detachment and facilitate transport of antigens and allergens across the epithelial barrier. In addition, Tomee et al. [43] showed that human bronchial and alveolar epithelial cell lines produce large amounts of pro-inflammatory cytokines and chemokines (IL-6, IL-8 and monocyte chemotactic protein (MCP)-1) when incubated with *A. fumigatus* proteases, inducing additional epithelial activation. This activation process is partly dependent on protease-activated receptor 2 [44]. Moreover, the spectrum of response to recombinant *A. fumigatus* allergens suggests that some of them appear to be more strongly implicated in both *Aspergillus* sensitisation and ABPA [45]. Several proteases also have immunogenic properties [9]. Eosinophils are major cells causing inflammation in ABPA and eosinophil proteases and proteins may enhance epithelial destruction.

Induction of a Strong Th2-CD4$^+$ T Cell Response, Characterised by a "Hypersensitivity to IL-4"

AF releases allergens during hypheal growth and more than 60 structures of AF are susceptible to bind IgE, and genetic analysis of Aspergillus species identified 30 allergens, including proteins, polysaccharides, glycoproteins, proteases (Aspf5, f10, f13, etc.…), glycosidases (Aspf2, 9…) and many proteins produced or secreted, some being involved in oxidative stress. ABPA occurs in immune-competent subjects and dysfunction or specific polymorphisms of genes encoding for the Toll-Like receptor (TLR)-2, 4 or 9 involved in recognition of specific AF motifs are not demonstrated in ABPA [21]. Allergens are processed by antigen-presenting cells and presented to T cells. ABPA is characterised by a strong Th2 CD4 response with two main consequences: the release of large amounts of IL-4 and IL-5 (and also IL-13), which explains the influx of eosinophils and hyper-IgE production namely during exacerbation episodes, as well as activation of B cells [46–50]. Lymphocyte activation has been shown in humans and in animal models [46–52]. In mice challenged with AF, there is an accumulation of pulmonary Th-2 cells with a higher number of granulocyte-macrophage colony-stimulating factor (GMCSF)-, IL-4- and IL-5-positive cells in the ABPA murine model than in controls [53], while IL-10 seems to act as a natural suppressor of the pro-inflammatory reaction [54, 55]. Nevertheless, regulating mechanisms are complex when there is an association between the −1082GG genotype of IL-10 promoter (increasing IL-10 synthesis) with AF colonisation and the development of ABPA in CF [56]. In patients with ABPA, peripheral blood mononuclear cells showed increased sensitivity to IL-4 [57]. IL-4 is involved in IgE production, but also eosinophil activation, via up regulation of very late antigen (VLA)-4 and C chemokine receptor (CCR)3 expression [57, 58]. Elevated blood sIL-2 receptor concentrations and higher levels of cluster differentiation (CD)23 expression on B cells were found in ABPA patients [59].

Compared with *A. fumigatus*-sensitised asthmatics without ABPA, the increase in CD23 expression is also partly mediated by IL-4 [60]. Recently, Hartl et al. [61] evaluated pro-Th2 chemokines in ABPA in patients with CF. Th2 cells preferentially expressed the chemokine receptor CCR4 and were attracted by the corresponding chemokines, thymus and activation-regulated chemokine (TARC) (CCL17) and macrophage-derived chemokines (MDC). The levels of TARC were elevated in ABPA when compared with atopic controls or CF without ABPA: these values increased significantly during acute exacerbations of ABPA, in parallel with total IgE levels. It is interesting to relate these data to the experimental study by Schuh et al. [62]: the CCR4 knock-out mouse model exhibited reduced bronchial hyperresponsiveness and more rapid clearance of AF, indicating a major role for CCR4 and TARC in the immune response to AF. Elevated serum TARC may be useful in CF patients for diagnosing ABPA [63]. TARC may link an antifungal immune response with the promotion of Th2 cells and hypersensitive response to AF [61].

Another indication of increased IL-4 sensitivity in ABPA was provided by Knutsen [64]: he studied the presence of IL-4 receptor α-chain single nucleotide polymorphisms (SNPs) in ABPA and showed that IL4R α chain SNPs were observed in 95 % of ABPA, with a predominance of extracellular IL-4R α SNP "ile75val", present in 88 % of ABPA. The latter study suggested that this polymorphism might be a genetic marker of ABPA risk. Thus, IL-4 "hypersensitivity" is clearly involved in the amplified IgE response, and may play a major role in the B-cell hyper-reactivity in ABPA [37].

Amplification of the B-Cell Response

Amplification of the B-cell response: large amount of total serum IgE. The T-cell response in ABPA patients was associated with B-cell activation and the presence of large amounts of IgE, IgA and IgG in the blood and bronchial lumen [65]. Divergent results were obtained in studies of blood and bronchoalveolar lavage (BAL) fluids concerning the production of immunoglobulins directed against *A. fumigatus*. Such inconsistencies may be explained by differences in the detection methods used: some authors evaluated precipitating antibodies, whereas others used enzyme-linked immunosorbent assay (ELISA) or radio-immunoassay (RIA) methods.

Moreover, the quality of antigen extracts differed considerably between studies. The use of recombinant antigens should improve detection rates and make the results of these studies more reproducible and reliable. The IgE response is largely, but not exclusively, directed towards *A. fumigatus* epitopes [66]. Indeed, mould AF contains abundant carbohydrates, including glycan, chitin and galactomannan. In mice sensitised with AF extracts treated by sodium-periodate that destroys carbohydrates, a significant decrease in both total and specific IgE was obtained, as well as a reduction in eosinophil recruitment. Indeed, carbohydrates present in ABPA play a key role as internal adjuvants in the total IgE response [67].

Tissue Damage

Tissue damage (bronchiectasis formation) occurs in ABPA patients as a consequence of the local influx of neutrophils and eosinophils. Sputum eosinophil and neutrophil counts are higher in ABPA patients with bronchiectasis than in those without bronchial destruction [68]. The extent of bronchiectasis, detected by high resolution computed tomography (CT) scan, correlates with the number of eosinophils and neutrophils in the sputum, but not with total IgE levels in the serum [68]. Recently, Gibson et al. demonstrated that IL-8 gene expression and IL-8 protein levels in the sputum were higher in ABPA patients than in controls, and the extent of these two parameters correlated with the degree of bronchial neutrophilia and airway obstruction [69]. Thus, IL8 may be a key mediator of tissue damage in ABPA.

Diagnosis

ABPA is defined by major diagnostic criteria – clinical, biological and radiological criteria – but definition remains debated and particularly difficult in CF patients (Tables 5.2 and 5.3) [9, 70–73].

Clinical Vignette

A 64 year old woman was referred to hospital for acute exacerbation of asthma.

Asthma was diagnosed at the age of 19 and "disappeared" during her 20s. At the age of 39, recurrence of asthmatic symptoms (coughing, wheezing, nocturnal symptoms) was observed. Since 6 years, asthma was controlled by formoterol and fluticasone (250 mg × 2/day), and salbutamol "as-needed". Lung function tests performed 6 years-ago showed bronchial obstruction (a decrease FEV1 : 78 % of predicted value, with normal FVC : 98 % PV), which return to normal value after 1 month of inhaled treatment (FEV1: 92 % PV). The chest X-ray was normal. Skin prick tests showed sensitisations to *Dermatophagoides pteronyssinus*, cats, horses, *Cladosporium sp.* and *Aspergillus fumigatus*.

When admitted for acute exacerbation, the patient complained of frequent respiratory symptoms over the previous 8 months. She had required oral corticosteroids on six occasions in the previous 8 months, some-

Table 5.2 Diagnostic criteria for ABPA (not CF patients)

Classic case to diagnose ABPA in CF (minimal diagnostic criteria in red)
1-Acute/subacute clinical deterioration not attributable to another etiology
2-Total serum IgE level>1000UI/mL (or 2400ng/mL) (without corticosteroid treatment) Total serum IgE level>500UI/mL. If ABPA is suspected and the total IgE level is 200-500IU/mL, repeat testing in 1-3 months.
3-Immediate positive skin prick test for AF or the presence of serum specific IgE to AF
4-precipitating antibodies or serum IgE to AF or 5-Chest radiological changes on radiography or CT, not cleared with antibiotics and standard physiotherapy

In red: minimal criteria to diagnose a seropositive ABPA (ABPA-S); If we add "central bronchiectasis" to the "red criteria", the diagnosis is ABPA-CB (for central bronchiectasis)

Table 5.3 Diagnostic criteria for ABPA in cystic fibrosis patients [9] (consensus conference recommendations for diagnosis for ABPA in CF). The classic diagnostic criteria for ABPA are in black text. The minimal diagnostic criteria for ABPA are written in red

1-Acute/subacute clinical deterioration not attributable to another etiology
2-Total serum IgE level>1000UI/mL (or 2400ng/mL) (without corticosteroid treatment) Total serum IgE level>500UI/mL. If ABPA is suspected and the total IgE level is 200–500IU/mL, repeat testing in 1–3 months
3-Immediate positive skin prick test for AF or the presence of serum specific IgE to AF
4-precipitating antibodies or serum IgE to AF or 5-Chest radiological changes on radiography or CT, not cleared with antibiotics and standard physiotherapy

times associated with antibiotics. She had dark sputum. Sometimes, she experienced right or left chest pain, increased by inspiration. She had no extra-respiratory manifestations.

On admission, the patient was febrile (39 °C), despite a treatment-associated amoxicilline-clavulanic acid and ciprofloxacin over the previous 72 h. She had not taken any oral steroids at that time. The chest auscultation showed crackles with reduced breath sounds in the left apical area and diffuse wheezing. She complained of left axillary chest pain. Sputum was purulent and brown.

Investigations showed:

- An inflammatory syndrome: C-reactive protein: 67 mg/l
- A blood eosinophilia (1,900 elements/mm^3) and neutrophilia (8,200 elements/mm^3)
- Normal renal and liver laboratory tests
- A high blood total IgE level (2,800 UI/ml)
- No detection of blood anti-neutrophil cytoplasmic antibodies (ANCA)
- Normal cardiac ultrasound was normal.
- Upper left lobe atelectasia on the CT scan (Fig. 5.2a, b)
- No new sensitisations on the skin prick tests, compared with previous ones

Diagnosis of ABPA was presumed (asthma with "atypical symptoms", pneumonia resistant to treatment, eosinophilia, elevated total IgE and no argument for a vasculitis).

- Specific IgE assay against *Aspergillus fumigatus* antigen by Phadia CAP System (Kabi Pharmacia, Sweden) was positive (24 UI/mL).
- An enzyme-linked immunosorbent assay for *Aspergillus-specific* IgG antibodies showed a titer of 3.98 indices.
- An immunodiffusion precipitin test to detect *Aspergillus-specific* antibodies demonstrated a positive result (6 precipitin bands).

The patient was trea ted with steroids (0.5 mg/kg/day; e.g. 25 mg/day), physiotherapy and nebulisation of saline isotonic solution. After 4 days of treatment, the fever and the blood eosinophilia disappeared. FVC and FEV1 were respectively 68 % and 45 % of predicted values. The radiological

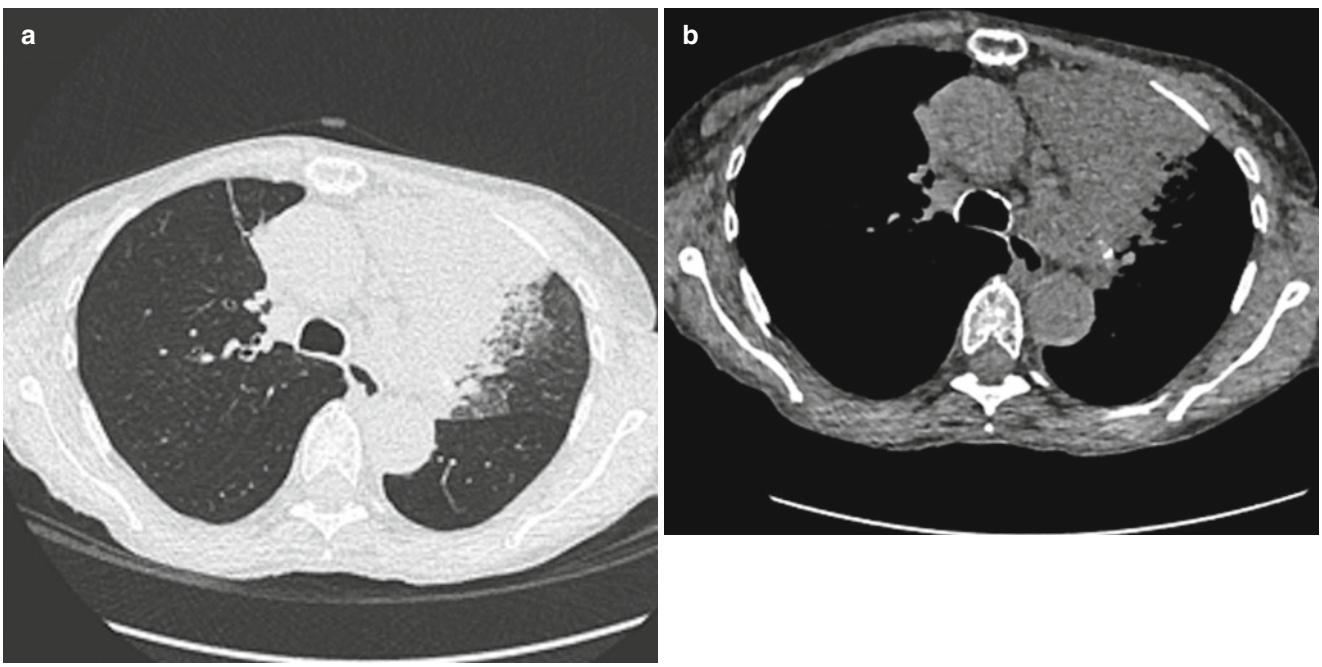

Fig. 5.2 (**a**) Parenchymental section and (**b**) mediastinal section: CT scan showing isolated upper left lobe atelectasia

aspect was not modified and flexible bronchoscopy was indicated. A voluminous mucus plug was obstructing the upper left bronchus, collecting multiple mucoid impactions after bronchio-alveolar lavage. AF hyphae were detected in BAL when other explorations were negative (bacterial and mycobacterial analysis).

After 7 days, the patient came out of hospital with a final diagnosis of sero-positive ABPA.

The detection of AF hyphae has led to treatment associated itraconazole (400 mg/day) and oral steroids (25 mg/day) for 2 weeks being proposed, then a slow decrease for a total period of 8 weeks). After 4 weeks, total IgE level was 740 UI/mL. She had no further sputum and chest pain. The inhaled treatment (fluticasone and formoterol association) was stopped.

The patient has been monitored in our institution for 6 years now and is still under itraconazole. When we tried to stop itraconazole on three occasions, a new exacerbation of ABPA occurred, with atelectasia or lung infiltrate, marked increase in total blood IgE, requiring high doses of steroids. Courses of steroids were prescribed seven times throughout these 6 years times. She still has blood total IgE ranging between 390 and 615 UI/mL.

– The occurrence of asthma with frequent exacerbations, but with "atypical" symptoms of asthma led to discussion of an alternative diagnosis, particularly ABPA in this case.

Clinical Symptoms

The ABPA is more frequent in young adults between 30 and 40 years old. It can occur in childhood, but is less frequent during this period. In CF patients, it is recommended that the patient be tested for ABPA once a year after the age of 6 [9]. Most patients have atopic asthma and more than 60 % of CF patients with ABPA are atopic. ABPA may occur at the time of the asthma diagnosis or, more often, after the onset of asthma. Asthma symptoms may change with fever (body temperature reaching 38.5 °C), malaise, chest pain, thick, purulent, sometimes brown sputum. There may have cough, haemoptysis. Pulmonary consolidation without bacterial or viral infection has been observed. Physical examination does not add any information for ABPA diagnosis. Crackles are present at the stages of destruction. The diagnosis must be discussed in asthmatic patients with frequent exacerbations and/or requiring recurrent corticosteroid courses and/or hypereosinophilia. In refractory asthma, the diagnosis of ABPA must be challenged. In children, when ABPA is diagnosed, sweet chloride tests must be performed.

Radiological Patterns and Pulmonary Function Tests

Radiographic analyses (Figs. 5.3a, b and 5.4a, b) have been carried out on chest X-rays and high resolution CT (HRCT) scans. Some abnormalities tend to be **transient**, such as pulmonary infiltrates, the presence of fluid in the bronchi and lobar or segmental collapse linked to mucous plugs [72, 73]. **Permanent patterns** included bronchiectasis, most frequently in the upper lobes in the segmental and

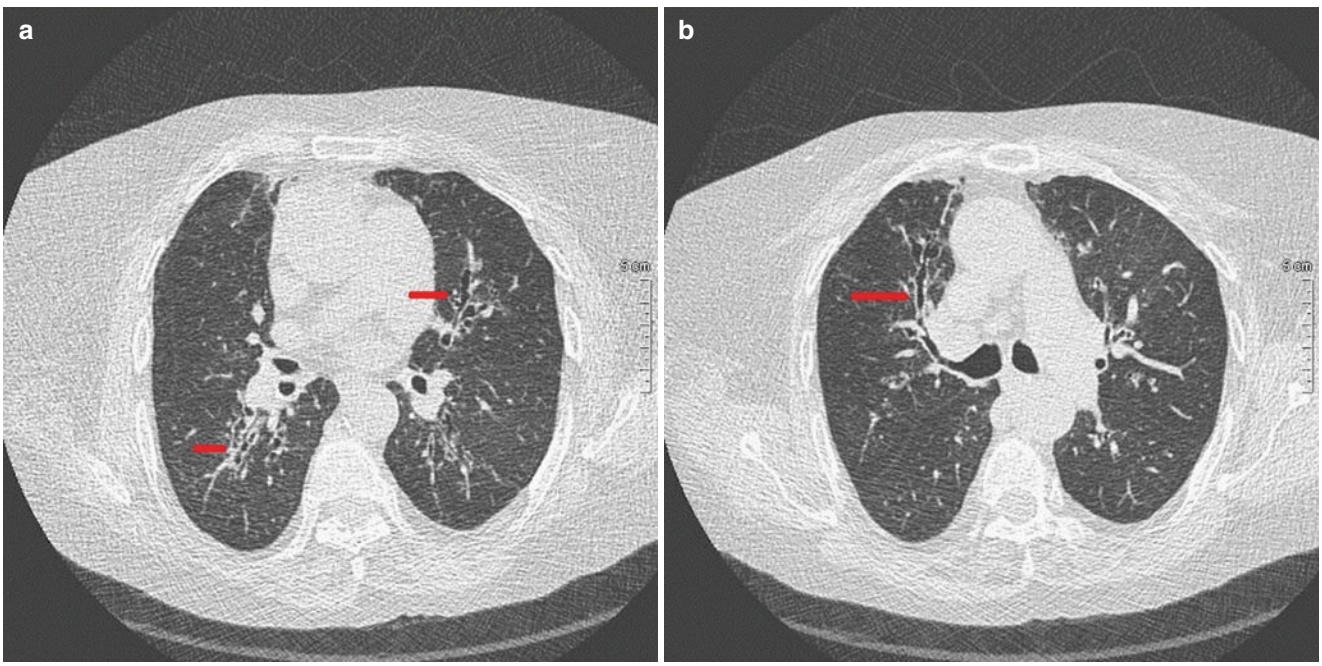

Fig. 5.3 (**a**, **b**) CT scan (lung window, 1 mm slices): proximal bronchiectasis (*red lines*) in a 62-year-old woman treated for bronchiectasis ABPA for 13 years

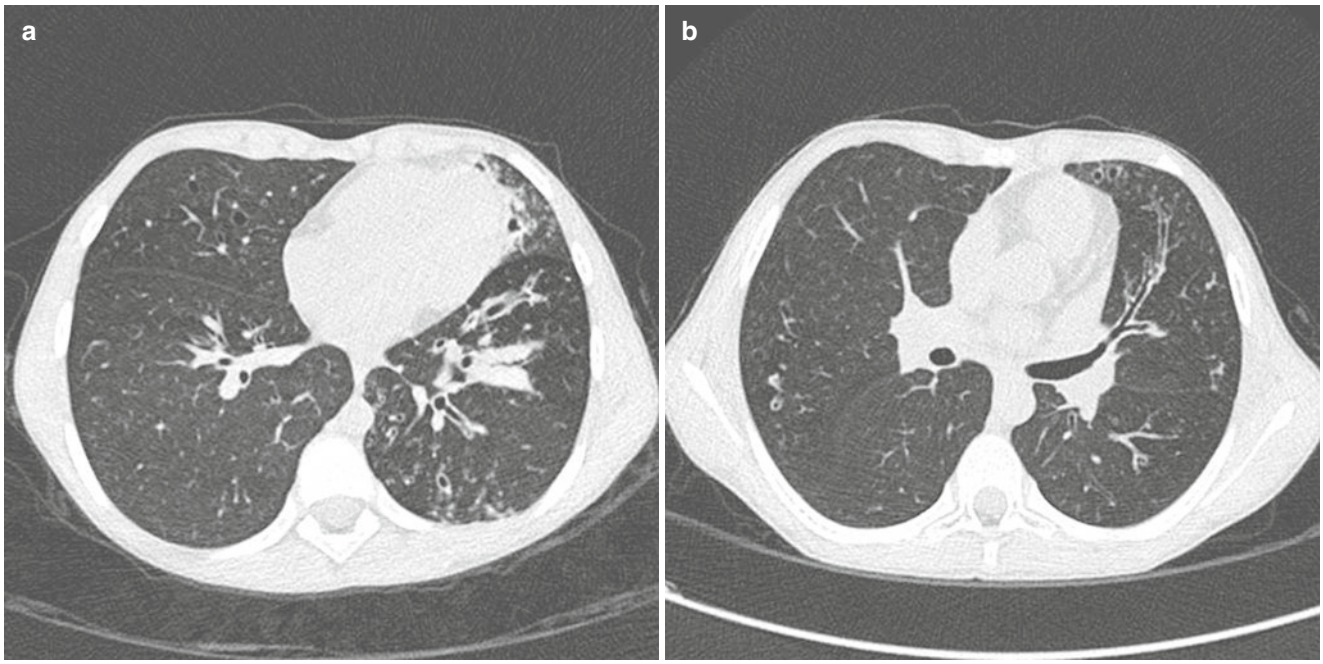

Fig. 5.4 (**a**, **b**) HRCT scan in a 13 years old girl with CF and ABPA: (**a**) tubular opacities and mucoid impaction (lower left lobe); (**b**) Bronchiectasis extending to the periphery with "finger in glove" appearance (lingula)

subsegmental bronchi, and cavities. HRCT scan was normal in 37 % of ABPA patients [74]. Bronchiectasis occurs at more central sites in ABPA patients than in those with other bronchial diseases. However, bronchiectasis has been reported in the peripheral airways in some ABPA cases [75, 76]. The presence of central bronchiectasis is not pathognomonic of ABPA and may have a low sensitivity, up to 37 % [76]. Analysis using plain film revealed that most patients (19/20; 95 %) had upper lobe abnormalities, but 9/20 had both upper and lower lobe involvement [77]. Descriptions of "glove-finger" opacities are common and correspond to bifurcating opacities caused by the bronchial distribution resulting from mucoid impaction. The collapse of a lobe segment, or an entire lobe, has been described and is often associated with clinical exacerbation. Recurrence of mucoid impaction in these segments is not rare and may predispose the patient to bronchial damage. High-attenuation mucoid impaction should be suggestive of ABPA [17, 78, 79] and recent data showed that it was associated with a more intense immunological activity [75].

Pleural effusion or calcifications of mucoid impactions are rare but have been reported [80]. Pulmonary fibrosis, pneumothorax and cavities occur during end-stage ABPA [76, 77, 81].

High-resolution CT scan is more sensitive than chest X ray for the detection of transient pulmonary infiltrate or bronchiectasis. Bronchiectasis patterns are described as cylindrical in most cases, but have also been referred to as cystic or varicose [81, 82]; Several studies have compared abnormalities in ABPA patients with those in *Aspergillus*-sensitive asthmatics [8, 81–85]. One of those studies showed that bronchiectasis is common in ABPA but occurs only occasionally in asthmatic adults with a positive skin test to AF [83]. In that study, bronchiectasis was identified in 14/17 ABPA patients (82 %) with a large percentage of lobes (42 %) versus 2/11 (18 %) asthmatics sensitized to AF and a low percentage of lobes (5 %). In that study, pleural thickening in 14 (82 %) and atelectasis in 9 (64 %) were also described [83].

Respiratory function tests (expiratory flow rates, lung volumes and diffusion capacities) are useful for diagnosis and during follow-up, but alone are not sufficient for monitoring treatment. Obstruction and restriction are both aggravated during acute exacerbations. Reductions in lung volume and diffusion capacity have been observed during exacerbations and in patients with end-stage ABPA [4, 86]. The severity of the obstruction in corticosteroid-dependent asthma (stage IV) varies depending on the patient [87–89]. Deterioration of lung function also differs between ABPA patients; in some individuals, lung function remains stable, or is even improved in serologic ABPA (without bronchiectasis) [90], whereas in others, functional parameters progressively deteriorate [91]. In CF patients, ABPA is associated with a more severe progression of forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) [92]. Malo et al. compared the results of lung function tests of 20 asthmatic patients with ABPA with those of 20 asth-

matics, paired in terms of sex, age and duration of asthma [93]. All patients with ABPA and 75 % of patients with asthma alone showed significantly reduced FEV1. In contrast, FEV1 reversibility was more frequent in patients with asthma alone (50 %) than in those with ABPA (31 %), and the extent of this reversibility was also statistically higher in patients with asthma compared with those with ABPA [93].

Skin Tests and Biological Investigations

- Nearly all ABPA patients show an immediate cutaneous reaction to skin prick-tests with an *Aspergillus* mixture (aspergillus allergens extracts). The reactivity varies in time and may be influenced by the allergenic extracts. A dual reaction (associated immediate and late or delayed positive skin tests) is rare, involving about 16–33 % of patients [94, 95]. The delayed reaction is of little interest in ABPA diagnosis [94, 95]. Concerning the use of recombinant antigens in cutaneous testing, Hemmann et al. showed that skin prick tests with rAspf4 and rAspf6 provoked immediate skin reactions in patients with ABPA but not in controls, and therefore enabled discrimination between ABPA and sensitisation to *A fumigatus* [96].
- Patients may also have sputum and/or blood eosinophilia, particularly at the time of diagnosis or when exacerbations occur during periods when they are not receiving corticosteroids. In these situations, blood eosinophil levels may be high, between 1,500 and 3,000/mm^3 [95].
- *A fumigatus* can be detected in the sputum of 50 % of ABPA patients [95]. Examinations of two or more specimens increase the rates of positive culture [97]. *Aspergillus* PCR, more sensitive than culture, may be efficient in evaluating the effectiveness of antifungal therapy, but has poor interest in ABPA diagnosis [98]. The presence of hyphae is more specific than spores.
- The most reliable diagnostic tests are measurements of total serum IgE and serum IgE- and IgG- specific antibodies as well as the determination of the presence of *A. fumigatus* antibody precipitins (results expressed as the number of precipitation lines). It generally shows two or more precipitation lines, to one or sometimes more extracts [99]. Extracts differ between laboratories. Some *Aspergillus* antigens (catalase, trypsine, chymotrypsine) are essential for these reactions. These enzyme activities can be detected after gel diffusion and, as these antigens appear to be specific to *A. fumigatus*, may be useful for diagnosis [100]. Variations in levels of specific antibodies are a function of treatment, age and stage of ABPA [101–103]. Total serum IgE levels are high in ABPA patients, usually greater than 1,000 IU/mL and decrease when they are in remission as a result of corticosteroid treatment. This decrease occurs within 2 months after initiation of corticosteroid treatment. Total serum IgE levels sometime return to within the normal range during the end-stage [101].
- Approximately 60 epitopes able to bind the IgE molecules have been identified from *A. fumigatus*, alongside more than 20 recombinant allergens (named Aspf1 to Aspf22) [99]. Studies suggest that some of the recombinant allergens may be useful for discriminating between individuals with ABPA and those with AF-sensitised asthma [45]. Kurup et al. assessed the abilities of recombinant *Aspergillus* allergens (Aspf1, f2, f3, f4, and f6) from the sera of ABPA patients and *A. fumigatus*-sensitive asthmatics to bind to IgE: the number of recombinant allergens able to bind to the IgE antibody was higher in sera from patients with ABPA than in those of the asthmatics. Aspf2, f4, and f6 interacted with IgE in all ABPA patients tested [45]. Such binding tests could therefore be used in ABPA diagnosis. In contrast, IgE antibodies binding to Aspf1 and f3 were not specific. Several studies compared the respective responses in terms of specific IgE antibodies towards the recombinant *A. fumigatus* antigens (mainly Aspf2, f3, f4, f6 and f16) in asthmatics sensitised to *A. fumigatus* and in ABPA patients with or without CF. Current results show some discrepancies. Crameri et al. reported higher IgE levels to rAspf4 and f6 in ABPA patients when compared with asthmatics sensitised to *Aspergillus* [104]. The same group showed that specific IgE to rAspf1 and f3 represented a marker for sensitisation, while specific IgE antibodies rAspf4 and f6 gave an indication for ABPA which was clinically confirmed [105].

Hemmann et al. also reported higher IgE levels to Asp f4 and f6 in ABPA CF patients [105]. Another study analysed the position of different recombinant antigens in their binding to IgA, IgG and IgE antibodies in patients with CF alone or associated with ABPA [106]. Present data suggest that no antigen (rAspf1, 2, 3, 4, 6), antibody isotype or method is capable of differentiating CF with or without ABPA, although some allergens show a higher prevalence of strong reactions. Recombinant allergens, rAspf1, rAspf2, rAspf3, rAspf4 and rAspf6 and recently rAspf34 have been evaluated to differentiate ABPA from asthma-sensitised to AF and mainly to diagnose ABPA in CF [63, 106–108]. Banerjee et al. showed that 70 % of patients with ABPA had high levels of serum IgE antibodies to Aspf16, a 43 kDa protein, whereas patients with positive AF skin test did not [109]. Specific serum IgE from rAspf4 and rAspf6 seems to be detected only in ABPA, but other studies did not show this [110]. The sensitivities obtained seem to be higher with rAspf4 [107, 111]. Only Latzin [63] showed a higher sensitivity with rAspf6 compared with rAspf4; rAspf6 is specifically expressed in hyphae, which might explain a preferential IgE response to rAspf6 in ABPA patients [112].

Two additional points must be discussed in patients with ABPA: amplification of the total IgE response appears to be associated with the presence of abundant amounts of carbohydrates present in the mould *Aspergillus*, but carbohydrates only act as an adjuvant and are not the target of the induced IgE response [67]. Similarly, the kinetics of the antibody response to recombinant antigens in ABPA patients showed serum levels of specific IgE 16–18 times higher than rAspf4 and f6, but follow-up of the specific IgE response was of limited value for guiding therapy [113]. To conclude, even if rAspf2 and rAspf4 and rAspf6 are more often associated with ABPA, their lack of specificity do not yet permit to use them in clinical routine, in asthma as in CF If recombinant allergens are available, their usefulness in the diagnosis work up needs to be confirmed.

Other markers such as TARC, elevated in CF patients with ABPA, are not routinely evaluated.

Pathology of ABPA

Although pathological specimens are obviously not necessary for diagnosis, when bronchial samples were studied, the bronchial tree was dilated and filled with mucus plugs containing macrophages, eosinophils, Charcot-Leyden crystals and sometimes hyphae or hyphal fragment [114, 115]. Bronchial walls were infiltrated with inflammatory cells (eosinophils, lymphocytes and plasma cells); a thickening of the basement membrane along with epithelial abrasion was also found. The pathology of the peribronchial areas and parenchyma is sometimes different from that described above: bronchocentric granulomatosis with bronchial remodelling and dilation has been described as being a complication of ABPA [116]. However, bronchocentric granulomatosis is clearly a particular entity associated with a different pseudo-tumoral radiological pattern and possibly with other conditions such as tuberculosis, inflammatory disease of the bowel and rheumatoid arthritis [117]. Infiltration of the parenchyma with mononuclear cells, eosinophils and lymphocytes leads to inflammation that mimics or is associated with patterns observed in individuals with other forms of interstitial disease such as granulomatous bronchiolitis, exsudative bronchiolitis or obliterans bronchiolitis [118]. Micro-abscesses with *Aspergillus* hyphae and granulocytes have also been described in the parenchyma of ABPA patients, demonstrating that the frontier between invasive and allergic manifestations is sometimes poorly delimited.

Diagnostic Criteria and Stages in Asthmatics and in CF Patients

The diagnosis of ABPA is based on the presence of a combination of clinical, biological and radiological criteria.

When the patient is under corticosteroids, some parameters can be modified: disappearance of pulmonary infiltrate, of blood eosinophilia, and decrease of total IgE and antigens directed to AF. For these reasons, it is sometimes useful to re-test the patient at distance from systemic corticosteroids.

In asthma, bronchiectasis involving the more central segmental bronchi is a strong diagnostic criterion, but is not always present in patients during follow-up or at the time of diagnosis. Greenberger identified two groups for differentiating ABPA patients, with and without bronchiectasis [119]: ABPA with central bronchiectasis and seropositive ABPA without bronchiectasis. The "major" and "minor" criteria are challenged, because the value of these criteria is not established (positive and negative predictive values). For this reason, minimal criteria to diagnose ABPA should be retained (Table 5.2). Kumar et al. [120] studied the characteristics of ABPA patients and found that patients could be divided into three groups: ABPA with positive serology **(ABPA-S),** ABPA with central bronchiectasis **(ABPA-CB)** and ABPA with central bronchiectasis and other radiologic features **(ABPA-CB-ORF)**. Pulmonary function abnormalities were mild in the ABPA-S group, moderate in the ABPA-CB group and severe in the ABPA-CB-ORF group. Absolute eosinophil counts rose in each group, but were highest (1.233/ml) for the ABPA-CB-ORF group. The levels of *A. fumigatus-specific* IgE followed the same pattern, with a maximum of 47.91 KIU/L for the ABPA-CB-ORF group. Symptom scores were also higher for the ABPA-CB-ORF group than for the other groups. Thus, the ABPA-S group probably comprised patients at an early stage or with a less aggressive form of ABPA. Studies by Greenberger et al. [99, 119] led them to suggest that early recognition and treatment of ABPA may prevent progression to end-stage ABPA. A recent study [17] evaluated 564 patients with asthma screened for *Aspergillus* with skin tests. 223 (39.5 %) had positive AF skin tests. ABPA was diagnosed in 126 patients (27 %). Among this population, there was 27 % ABPA-S, 33 % ABPA-CB and 40 % ABPA-CB-ORF with radiological findings. An interesting point is that there was no difference between the stage of ABPA and the severity of asthma, the duration of illness or serologic findings. However, tuberculosis was diagnosed in the past in 46.8 % of this population [17]. For this reason, these data cannot be superimposed on countries with low-endemic tuberculosis.

In CF patients: ABPA is a common complication of this disease, occurring in approximately 10 % of cases. Diagnosis of ABPA in CF patients is difficult for several reasons. Some of the criteria used for ABPA diagnosis are common manifestations of CF. CF patients often present exacerbations with bronchial obstruction, pulmonary infiltrate and bronchiectasis [9, 121]. In addition, CF patients may develop immune responses to *Aspergillus* (IgE, IgA, IgG antibody production, elevated total serum IgE levels) in the absence of ABPA. The

Table 5.4 Stages of ABPA

Stage	Clinical characteristics	Biology	Radiology
I: Acute	Fever, cough, chest pain, hemoptysis, sputum	Elevated total serum IgE +++ levels, (+/−blood eosinophilia)	Pulmonary infiltrate (s) (upper/middle lobes)
II: Remission	Asymptomatic/stable asthma	Normal or elevated total serum IgE + levels	No infiltrates, in the absence of systemic corticosteroid therapy for >6 months
III: Exacerbation	Symptoms mimicking the acute stage or asymptomatic	Elevated total serum IgE +++levels, (+/−blood eosinophilia)	Pulmonary infiltrate(s) (upper/middle lobes)
IV: Cortico-dependent asthma	Persistent severe asthma	Normal or elevated total serum IgE + levels	With or without pulmonary infiltrate(s)
V: Fibrosis (end-stage)	Cyanosis, severe dyspnea	Normal or elevated total serum IgE + levels	Cavitary lesions, extensive bronchiectasis, fibrosis

According to Patterson et al. [13]

boundary separating these biological responses from those involved with ABPA is extremely difficult to define [122–124]. Recently, the CF Foundation has proposed a new set of criteria for ABPA diagnosis in CF patients [9] (Table 5.3). These criteria are particularly valuable for diagnosis in cases where the condition of the patient has only slightly improved, or not improved at all, after appropriate treatment for bacterial bronchial infection. It is recommended that CF patients be screened for ABPA (serum total IgE, specific IgE/AF and precipitins/AF) from the age of 6, once a year or in response to the clinical suggestion of ABPA [9]. The prevalence of ABPA was low in patients under 6 years of age. In the European epidemiological study reported by Mastella et al., ABPA was more common in patients with a poorer clinical condition (lower FEV1, higher rate of microbial colonisation, poor nutritional status) [12]. Most of these patients had a delta f508/delta f508 genotype [12]. Due to this strong association between CF and ABPA, it may be useful to perform sweet chloride tests on patients showing signs of ABPA. In some patients, CF was diagnosed at the same time as ABPA [125].

ABPA progresses in five stages, which are not consecutive in time [13, 99] listed in Table 5.4. Treatment differs depending on the ABPA stage. Patients with acute exacerbation respond to corticosteroids and early treatment of pulmonary infiltrate with these drugs may prevent bronchial or bronchiolar destruction. Long-term treatment with corticosteroids is not recommended because this treatment does not prevent the emergence of new infiltrates or progression to fibrosis. Measuring total serum IgE levels is helpful for monitoring the treatment regimen. Total serum IgE levels are high during the acute and exacerbation phases of ABPA. By the end-stage, prognosis and treatment resemble those for CF patient management: patients have extensive bronchial destruction and the bronchial tree may be colonised by *Staphylococcus aureus* and/or *Pseudomonas aeruginosa*. Response to corticosteroids is limited at this stage. However, progression from stage I to stage V is not unavoidable and progression from stage IV to V is particularly uncommon.

Differential Diagnosis or Overlap Syndrome?

Asthma with Fungal Sensitisation

The main difficulty is differentiating between asthma with fungal sensitisation and ABPA. About 20–25 % of patients with persistent asthma are sensitised to one or more fungi [30, 126–128]. Among 1,132 asthmatics, sensitisation to *Alternaria* or *Cladosporium* increased the risk of severe asthma [129]. Adults with asthma having been admitted to hospital for acute asthma at least twice were more likely to be skin-test positive for at least one of the moulds AF, *Penicillium notatum*, *Cladosporium herbarum*, *Alternaria alternata* or *Candida albicans* (76 %) compared with mild to moderate asthma-sufferers (16–19 %; p, 0.0001) [130]. Another study also showed a doubling of the frequency of mould-positive radioallergosorbent tests (RASTs) in the moderate and severe groups (FEV1: 31–35 % of predicted value) compared with mild and no asthma controls (17–19 %; p = 0.01). *A. fumigatus* detection in sputum of asthmatics is associated with *A. fumigatus*-IgE sensitisation, neutrophilic airway inflammation and reduced lung function (FEV1 and FVC) [131]. The borderline between asthma and seropositive ABPA is sometimes difficult to identify when more than 10 % of asthmatic patients have precipitins directed/AF [132]. At least, one study showed that anti-fungal therapy may improve asthma in patients sensitised to AF [133]. This study and the high rate of AF sensitization in severe asthma explain that the term "severe asthma associated with fungal sensitization" (SAFS) is now discussed [133].

Allergic Aspergillus Sinusitis

The symptomatic search for sinus localisation is recommended. In a series of 95 patients with ABPA, Shah et al. [134], showed radiological evidence of sinusitis in 22 cases and confirmed, by antral wash or a surgical approach, the presence of *Aspergillus* in 7 cases. The same group [135]

recently reported the coexistence of ABPA, allergic *Aspergillus* sinusitis and aspergilloma in the same patient, an association that we also observed in two patients some years ago (personal unpublished data). Bone erosions are described on CT scan and specific ear-nose-throat (ENT) evaluation is required.

Hypersensitivity Pneumonitis (HP)

HP is an interstitial lung disease, that may result of an immune reaction (type III and IV hypersensitivity) to inhaled fungi (*Penicillium fusarium*, *Trichosporon*… and also Aspergillus species, such as AF, *A clavatus*, *A versicolor*). Most HP related to fungi occur in an occupational setting. HP related to *A clavatus* and *A fumigatus* are well described in the "malt-worker's lung" and AF is implicated in farmer's lung, salami brusher's lung, and in HP in tobacco industries [136–138]. Except for the summer-type HP causes by *Trichosporon* species in Japan, HP related to domestic fungi exposure is rare [139, 140]. Chronic HP caused by AF because of domestic leaky walls, resulting in lung fibrosis has been recently reported in Japan [141]. Implication of fungi have also been discussed in "humidifier lung", but the role of endotoxins and bacteria are also mentioned [142]. Insidious or acute presentations are reported, depending on the intensity and duration of exposure. Clinical symptoms (malaise, sweating, myalgia, loss of weight, and/or dyspnea), associated with micronodular and/or ground-glass opacities on CT scan in a particular environment and the identification of serum precipitins to AF extracts (usually present), or other fungi lead to diagnosis [143]. Serum precipitins to mould antigens have a controversial value for HP diagnosis. Fenoglio et al. suggest, with the aim to improve their diagnostic value, to use serological scores with a panel of relevant antigens [144]. Removal of the patient from exposure, and corticosteroids for severe patients usually lead to prompt resolution.

Aspergilloma, Chronic Necrotising Pulmonary Aspergillosis and Invasive Aspergillosis

Aspergilloma, chronic necrotising pulmonary aspergillosis and invasive aspergillosis are the main differential diagnoses. The host immune status and the clinical history are essential for specific diagnosis. These patients may have pulmonary infiltrate, sometimes blood eosinophilia and precipitins/IgE directed against *Aspergillus*. These diagnoses must be eliminated before prescribing corticosteroids. ABPA may also be complicated by aspergilloma and chronic necrotising pulmonary aspergillosis [145–147]. Chronic necrotizing aspergillosis (/aspergilloma) may be diagnosed at time or during the course of ABPA. In a recent study, Smith et al. showed that tuberculosis, non-tuberculous mycobacterial infection and ABPA remained the predominant risk factors for development of chronic pulmonary aspergillosis [148]. In ABPA, the role of systemic corticosteroid that may favour AF growth and infection by AF may be suspected [148]. There are some reports of ABPA that develop later, in pre-existing chronic necrotizing aspergillosis [149]

Finally, cases of tuberculosis (and non-tuberculous mycobacteria in CF) occurring before or during the course of ABPA have been described [17, 150].

Treatment and Course of the Disease

The long-term prognosis of ABPA is usually favourable, with most patients maintaining a good respiratory status. It is also related to the underlying disease, in case of CF. Nevertheless, patients with "refractory asthma" or bronchial destruction may develop permanent airflow obstructions and/or severe restrictions. Detecting exacerbations is essential for limiting airway destruction, but the long-term use of systemic corticosteroids is not recommended as there is no proof that this treatment prevents progressive bronchial destruction. In addition, exacerbations have been described in ABPA patients receiving high doses of oral corticosteroid [151], indicating that bronchial inflammation sensitive to corticosteroids is not the only factor involved in ABPA [152, 153]. Bronchial colonisation by fungal microorganisms represents an additional factor justifying the use of antifungal therapies. The goals of the treatment are:

- To limit exacerbations (requiring systematic testing for pulmonary infiltrates, which may or may not be associated with clinical symptoms).
- To eradicate colonisation and/or proliferation of *A. fumigatus* within the airway lumen and inside bronchiectasis and mucus plugs
- To manage cortico-dependent asthma and fibrosis

Thus, treatment appears to require two types of molecules: corticosteroids to treat the inflammatory response and antifungal agents to suppress or limit the proliferation of *A. fumigatus*, reduce antigenic stimulations and bronchial inflammation [153].

Treatment monitoring is based on:

- Clinical and radiological data
- Total IgE levels
- Drug plasma level (problems with absorption and bioavailability and drug-drug interaction with azole antifungal agents)

Oral Corticosteroids

- Systemic corticosteroids are currently the most effective treatment for the acute phase of ABPA. The recommended

dose is 0.5 mg/kg/day for the first 2 weeks, then on alternate days for 6–8 weeks, followed by a progressive decrease in dose over the next 6–8 weeks [99, 154]. The treatment is monitored by assessing symptoms (fever, chest pain, haemoptysis, acute wheezing, sputum production). However, monitoring must also include a chest roentgenogram or HRCT scan, as infiltrates do not lead to clinical manifestations in a third of cases. Repeated measurement of total IgE serum levels are also recommended every 6–8 weeks during the first year after diagnosis, to determine a base line value for each patient. A decrease in IgE levels of between 35 and 50 % or more is considered a good response. Increases in total IgE serum levels of more than 100 % above this base-line value indicate that the patient is at high risk of an exacerbation. A recent Indian study [17] suggests that higher doses and longer duration of oral corticosteroids may be associated with a better outcome. The treatment protocol proposed is a dose of corticosteroids of 0.75 mg/kg/day for 6 weeks, 0.5 mg/kg/day for 6 weeks, tapered by 5 mg every 6 weeks for a duration of 6–12 months [17].

In CF patients, an initial dose of corticosteroids may be higher: 0.5–2 mg/kg/day prednisone equivalent for 1/2 week (maximum 60 mg/j), 0.5–2 mg/kg/day every other day for 1–2 weeks, then progressively reduced within 2/3 months, according to the total IgE level, clinical and radiological status [9]. In acute ABPA exacerbation in CF, some case reports showed a benefit of monthly high doses of methylprednisolone pulse [155, 156]. The lung function tests recommended for asthma patients must also be performed, as reductions in lung volume, diffusing capacity or exercise tolerance may be associated with exacerbation.

In children, data are lacking, even in CF patients. A dose of 0.5–1 mg/kg/day prednisone equivalent for 10 days to 3 weeks, and then a rapid dose reduction should be tested. Long-term systemic corticosteroids are not recommended due to the adverse effects.

- In adults, long-term systemic corticosteroid therapy is also not recommended and thus assessment of clinical status, total IgE level and lung function is necessary for monitoring the treatment. If the patient has no further exacerbation within 6 months, he is considered in remission (stage II). Stage IV patients have severe asthma, which is corticosteroid-dependent. In these cases, the minimal dose required to stabilise the patient must be determined. Treatment preventing corticosteroid-induced osteoporosis must also be proposed if necessary. The extent of the bronchial destruction in stage V patients makes the prognosis poor. In addition, these patients suffer from recurrent infections (the majority of which involve *Pseudomonas*) and respiratory insufficiency with limited exercise tolerance. Treatment with corticosteroids is generally proposed, but is not very efficient. Lee et al. [91] assessed 17 patients with stage V ABPA (fibrotic stage) for a mean observation period of 5 years. Chest X rays infiltrates reoccurred in only one patient after initial diagnosis. All patients required long-term prednisone therapy for controlling asthma. The prognosis was poor for patients with FEV1 of less than 0.8 L after the initial corticosteroid treatment.

Antifungal Drugs

Several antifungal agents (i.e. amphotericin B, ketoconazole, clotrimazole, nystatin, natamycin) have been proposed as treatments for ABPA. However, no significant beneficial effects were observed with these drugs and, in several cases, they were even responsible for severe adverse effects [157].

In contrast, **itraconazole** appears to be an effective adjunct therapy for ABPA. Poor response to steroids, relapse, steroid-dependence and steroid toxicity are indications for itraconazole. Some years ago, we conducted a retrospective clinical study comparing the outcome of 1-year itraconazole treatment with that of 2-year therapy with systemic corticosteroids alone. Fourteen non-CF ABPA patients were included in that study and follow-up lasted for a period of 3 years. The following characteristics were compared: symptom scores, number of exacerbations, pulmonary function tests, total and *A. fumigatus*-specific serum IgE levels, the amount of corticosteroid required during the first 2 years by patients treated with these drugs alone and the amount required during the 1-year study period by patients treated with the itraconazole-corticosteroid combination. The number of exacerbations was lower for the itraconazole-treated group than for the group treated with corticosteroids alone. Corticosteroid daily requirements decreased from 22 to 6.5 mg/day, although the dose required differed substantially between patients [158].

Subsequently, the results of a 16-week randomised double-blind trial of twice-daily treatment with either 200 mg itraconazole or a placebo showed that itraconazole prevented disease progression in corticosteroid-dependent ABPA patients without any toxic effects [159]. A positive response was defined as a reduction of at least 50 % in corticosteroid dose, a decrease of at least 25 % in serum IgE concentration and one of the following: improvement of at least 25 % in exercise tolerance or pulmonary function tests, or partial clearance or absence of pulmonary infiltrates. In a second phase of the same trial, consisting of an open-label study, all patients received 200 mg of itraconazole per day for 16 additional weeks. In the double-blind phase of the trial, 46 % of patients in the itraconazole group responded to treatment, compared with 19 % in the placebo group ($p = 0.04$). About one-third (36 %) of the patients who did not respond during the double-blind phase responded to treatment in the open-label phase of the trial and none of the patients who responded in the double-blind phase of the

trial had a relapse [159]. The mechanisms underlying this treatment remain unclear. However, several data from a separate study suggested that itraconazole had an anti-inflammatory effect in the ABPA patients [153]: in this double-blind placebo-controlled trial involving ABPA patients with stable symptoms (n = 29) and receiving either 400 mg of itraconazole (n = 15) or a placebo (n = 14) for 16 weeks, results demonstrated that itraconazole treatment reduced eosinophilic airway inflammation, systemic immune activation and the number of exacerbations [153]. These results confirm that itraconazole can be used as a useful treatment for ABPA.

Meta-analysis of the data available (mainly three prospective, randomised and controlled studies) led to the conclusion that itraconazole modifies the immunologic activation associated with ABPA and improves clinical outcome, at least over a period of 16 weeks (Cochrane Airways Group Asthma Trial register) [160]. Treatment with this antifungal agent reduces bronchial inflammation and may prevent bronchial destruction and exacerbation in stable ABPA patients. It also improves the clinical status of cortico-dependent ABPA patients. Trials validating the use of itraconazole in ABPA patients used a dose of 200 mg × 2/day, administered for a duration of 16 weeks, then 200 mg/day for 16 weeks [160]. The initial dose of itraconazole in children is 10 mg/kg/day. Relapses occur after itraconazole cessation, making longer periods of treatment necessary [98].

There is a variable oral absorption and bioavailability of itraconazole. The solution may be superior to capsules. Capsules must be intake with a fatty meal while solution must be drunk on an empty stomach. It may be necessary to measure blood concentrations of itraconazole, after a minimum of 2 weeks of treatment, particularly if there are concerns about the lack of response and drug-drug interaction [161]. Some adverse events have been reported: adrenal suppression caused by inhalation of corticosteroids associated with itraconazole is a potential concern. Itraconazole, mainly via the cytochrome CYP3A4, interact with other drug metabolisms. It increases exposure to methyprednisolone, dexamethasone and inhaled budesonide [162–164]. Some additional side effects must be considered, mainly liver toxicity and peripheral neuropathy in cases of long-term treatment [165]. On the other hand, the hypothesis that the long-term prescription of antifungal therapy may lead to resistance is subject to debate.

Voriconazole has not yet been an indication for ABPA treatment, although it has been a useful adjunct therapy for ABPA in CF (CF) patients [166–168]. In 13 children with CF, voriconazole led to significant improvement in clinical and functional parameters. Adverse effects were reported, such as a photosensitivity reaction, nausea, a rise in liver enzymes and hair loss [167]. However, data concerning the benefit-risk ratio in ABPA are lacking and it cannot be recommended. Voriconazole could be an alternative in case of failure with itraconazole, particularly in CF patients.

Data concerning **posaconazole** in ABPA are missing, despite a retrospective positive study [169].

Other Treatments

Inhaled corticosteroids: the benefit of inhaled corticosteroids has not been demonstrated in ABPA. It is proposed for patients to control asthma but does not seem to have any effect on an ABPA course [170–173]. Considering the drug's interaction with itraconazole, beclomethasone or ciclesonide must be preferred [162].

Omalizumab: this monoclonal antibody directed against IgE has been used to treat ABPA in CF children [174, 175] and in non CF patients [176, 177]. Most studies reported beneficial effects of omalizumab in reducing exacerbation rates and doses of systemic steroids. In CF patients, FEV1 was also improved. These preliminary results are encouraging for pushing through a prospective double blind study.

Nebulised amphotericin; it has been suggested in case reports but there are no clinical trials [178].

There is **no place for immunotherapy**

The impact of long-term exposure to *Aspergillus* present in the environment is uncertain, but direct exposure to high concentrations of this fungus should be avoided. Decreasing indoor humidity and remediation of AF incursion improve air quality [179].

Fiberoptic bronchoscopy may be necessary to remove the mucoid impaction responsible for atelectasis in rare cases in which it is refractory to corticosteroid treatment.

Many Questions Remain Unresolved

- Patients with ABPA-seropositive and ABPA-bronchiectasis may represent different phenotypes of disease. Indeed, there is no longitudinal study proving that ABPA-seropositive is the first step leading inexorably toward destruction. These two forms of the disease should be possibly related to different pathophysiology or genetic backgrounds. And, in some cases, patients having pre-existing bronchiectasis with predisposing genetic factors (but not CF) should develop ABPA after AF colonisation and sensitisation, Other patients having asthma may develop ABPA without bronchiectasis. In our experience, the two phenotypes of the disease exist and patients with seropositive ABPA have a longer period of development, lower FEV1 and are older compared with bronchiectasis ABPA (partial results of an ABPA cohort, unpublished personal data).
- Specific tools for diagnosing ABPA, particularly in CF patients, are missing.

- The role of persistent environmental AF is also unresolved in ABPA development and evolution. Chronic AF infection may encourage the occurrence of severe forms of asthma, and of ABPA. AF can damage bronchial epithelium, encourage remodelling, and bear potent antigens. The respective role of persistent AF in airways (macrophages dysfunction, defective in AF clearance) and of chronic environmental exposure to AF in the occurrence of ABPA is unknown.
- Duration of treatments, doses of corticosteroids and itraconazole remain controversial. Optimising the antifungal treatment measuring itraconazole blood concentrations is also subject to debate.

Conclusion

ABPA is a common manifestation in chronic allergic asthma and CF patients. However, the delay in ABPA diagnosis is frequent. The role of genetic factors, particularly interacting with the epithelium functions and the Th2 immune response (IL-4 hypersensitivity), are essential for developing an ABPA. Different phenotypes of ABPA are described. Sero-positive ABPA and bronchiectasis ABPA may be the illustration of two stages of the disease, but also a different expression of the disease. When clinical, radiological and biological criteria for ABPA appear in combination and the diagnosis is made, then the treatment would need to include both systemic corticosteroids and the antifungal agent itraconazole. However, treatment regimens for this antifungal therapy have yet to be definitively established.

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Orphan Tracheopathies

6

Fabien Maldonado, Sara Tomassetti, and Jay H. Ryu

Introduction

Within the scope of respiratory medicine, central airway diseases have received overall less attention than parenchymal ones. This is perhaps based on the incorrect assumption that disease processes involving the trachea and main bronchi are relatively rare and most often clinically inconsequential. It is also likely secondary to the unfounded belief that severe cases may only be successfully managed by complex and invasive surgical interventions often associated with prohibitive surgical risks in this patient population. 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 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.

Anatomic Considerations

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

The trachea is an irregular tube that is mostly intrathoracic (lower two-thirds). It measures approximately 10 cm in adult females and 12 cm in adult males [1, 2]. In adults, the coronal and sagittal diameters measure on average 25 and 27 mm for males and 21 and 23 mm for females, respectively, with a lower limit of normal of 13 mm for males and 10 mm in females, respectively, in both axes [1–3].

Clinical Presentation

While stridor or a central, "monophonic" wheeze can occasionally suggest the diagnosis of tracheal disease, these symptoms are often reported late in the course of the disease and preceded by less specific symptoms of dyspnea on exertion, cough and, sometimes, hemoptysis. Tracheal diseases are unfortunately not always evident on plain chest X-rays and, as such, a high degree of 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 (CT) of the chest can now identify most tracheopathies and often suggest a precise diagnosis before definitive studies. In addition, chest CTs offer detailed information on the structures surrounding the airway, 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.

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Etiologies

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 emphysema. Malignancy may involve the trachea by direct endoluminal involvement, such as squamous cell carcinomas, adenoid cystic carcinomas or metastases, or indirectly by extrinsic compression from tumors arising from surrounding structures (e.g. esophageal carcinomas, thyroid carcinomas) or malignant lymphadenopathy. Likewise, 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 more infrequent diseases are occasionally encountered and often represent complex challenges for 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 [Wegener's], 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 progressive over the past 2 years. She was diagnosed with asthma several months ago and prescribed various inhalers (bronchodilators and inhaled steroids) without significant improvement. She is otherwise healthy, and is not taking 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. A chest X-ray is obtained and interpreted as normal. Pulmonary functions 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 gross tumoral infiltration. Biopsies are consistent with non-specific inflammation, without evidence of granulomas or malignancy. A diagnosis of idiopathic subglottic stenosis is established.

Tracheal stenosis may be encountered in a variety of different clinical situations. Tracheal trauma, whether related to prolonged intubation with excessive endotracheal tube cuff pressure, tracheostomy, infections (such as tuberculosis or *Klebsiella rhinoscleromatis, the agent associated with rhinoscleroma, a chronic and progressive inflammatory disease that involves the upper and, occasionally lower, respiratory tract*) or post-transplant (heart-lung, where the anastomosis is tracheal rather than bronchial) are notorious causes of secondary tracheal stenosis. Rarely, tracheal stenosis may occur as a complication of tracheal malignancy, radiation therapy, inhalational injury or even congenital causes (such as vascular ring or complete tracheal rings) [4–7]. 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.

The first case of ISS was described in 1972 by Brandenburg [8]. Since, few and relatively small case series have been published, and overall our understanding of the underpinnings of this rare entity remains limited. The vast majority of affected individuals are females, which has led to theories on the role played by the hormonal environment [8–11]. 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 [12]. While 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 [9]. The possibility of limited forms of granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) 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 limited GPA. In addition, biopsies of the upper airway will fre-

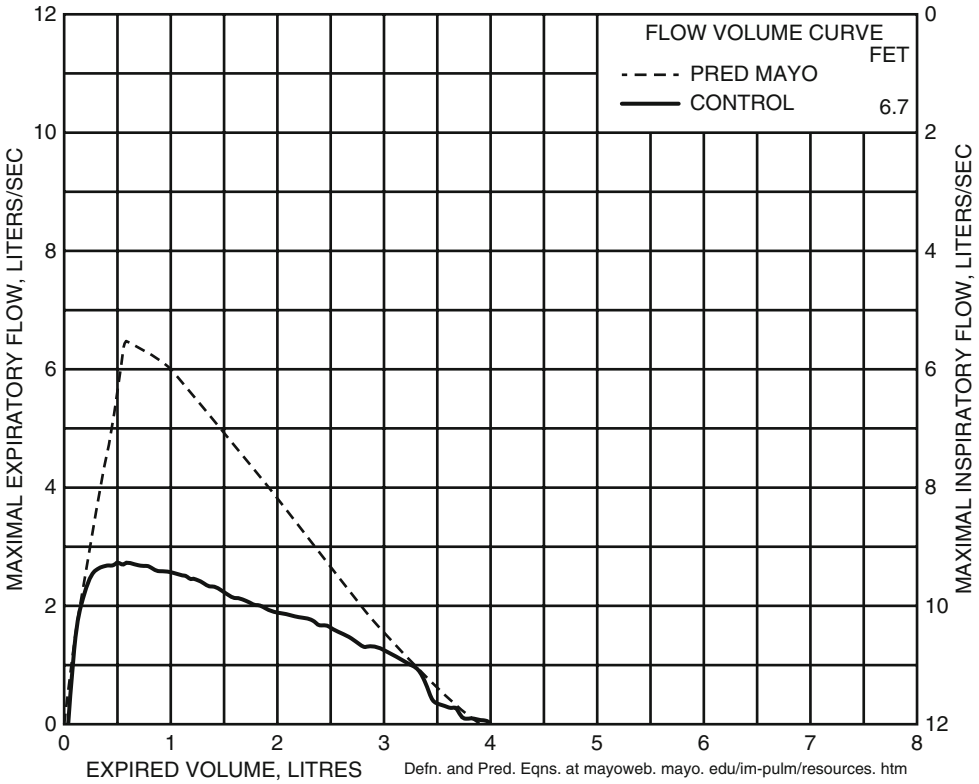

Fig. 6.1 The flow volume loop in fixed central airway obstruction reveals blunting of both the inspiratory and expiratory portions of the loop

quently 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 observation studies have reported a higher frequency of GERD in this patient population compared to the general population [7, 13–15]. Furthermore, treatment with antireflux agents has been associated with improvement in the severity of lesions observed and symptoms experienced by patients. More recently, an elegant case-control study 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 [16]. While causality remains in question, these observations suggest that GERD treatment should be at least considered as part of the management of these patients.

The most common symptom reported by patients with ISS consists of exertional dyspnea. The diagnosis is often delayed as symptoms generally occur late in the course of the disease, when stenosis compromises more than 50 % of the tracheal lumen. In addition, the possibility of central airway obstruction in patients without underlying risk factors is often overlooked and patients erroneously diagnosed with more common diseases such as asthma or chronic obstructive pulmonary disease. Late in the disease process, a monophonic wheeze or even stridor may become apparent.

Pulmonary function studies typically reveal an obstructive defect, with both inspiratory and expiratory plateaus on the flow-volume loop consistent with fixed central airway obstruction (Fig. 6.1).

Conventional chest X-rays are neither sensitive nor specific for the diagnosis of ISS. 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 three-dimensional reconstruction and virtual bronchoscopy images that can help define the type of stenosis (concentric, complex, hourglass) before invasive techniques. In addition, dynamic CT with expiratory views allows identification of dynamic collapse due to tracheomalacia occasionally associated with ISS [1, 2].

Bronchoscopy is the gold standard for the diagnosis of tracheal stenosis (Fig. 6.2). Typically, flexible bronchoscopy is used first in order to determine the location, extent and complexity of the stenosis. EBUS (endobronchial ultrasonography) can document the thickening of lamina propria of tracheal mucosa without cartilage involvement. This diagnostic tool can be helpful in both differentiating ISS from other diseases that usually involve 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

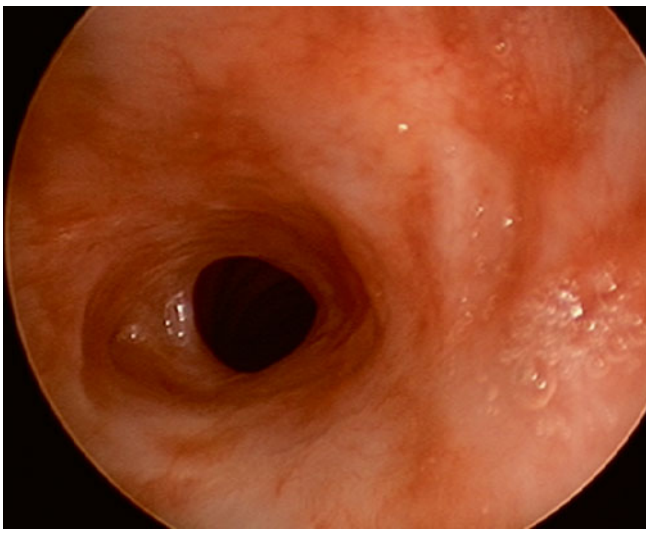

Fig. 6.2 Bronchoscopic view of idiopathic subglottic stenosis in a 38-year-old woman. The tracheal lumen is narrowed to 4 mm diameter

bronchoscopes may be used. In this situation, however, extreme caution is needed as edema or inflammation caused by the endoscopic procedure can result in life-threatening airway obstruction. In these cases, proceeding directly to rigid bronchoscopy may allow better management of the airway in a controlled operating room setting. High-frequency ventilation can be used with rigid bronchoscopy and is very 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 mucous glands and normal cartilage [12]. As mentioned above, studies evaluating the presence of estrogen and progesterone receptors have not been conclusive.

The definitive treatment of ISS consists of single-stage laryngotracheal resection with or without posterior membranous tracheal wall flap. The largest series published by Ashiku et al. 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 [17]. In contrast, the largest case series on endoscopic management of ISS reported recurrence requiring re-intervention in 30 % of patients at 6 months and 87 % at 5 years [18]. While the results would argue for surgical intervention in the majority of patients, it cannot be overemphasized that patients should be referred to centers of excellence with expertise in the management of this exceedingly rare disease. 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. Local applications of mitomycin C and/or intralesional injections of corticosteroids are sometimes used to prevent recurrences, though the evidence for this practice is scarce. In fact, some reports suggest that the excessive use of mitomycin C may be associated with subsequent tracheal stenosis from excessive fibroproliferation [19]. Airway stents are occasionally considered, but their use may be associated with recurrent tracheal trauma that could jeopardize future definitive surgical treatment. Tracheostomy is thought to present the same risks and is usually discouraged. The value of empiric medical therapy including inhaled steroids and empiric proton-pump inhibitor 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 lumina propria with preservation of the tracheal cartilage.
- By definition a diagnosis of exclusion, secondary causes of tracheal stenosis should be excluded

Tracheobronchopathia Osteochondroplastica

Clinical Vignette

A 55-year-old man is referred to urology for prostatectomy after being diagnosed with prostate adenocarcinoma. He is a never smoker but was diagnosed with chronic obstructive pulmonary disease a few years before and uses a beta-2-agonist inhaler on an as-needed basis as well as inhaled steroids. He has moderate obstruction on his pulmonary function test but his diffusing capacity is normal. He is considered 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 during endotracheal intubation before the procedure, 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.

With less than 400 cases reported in the literature, tracheobronchopathia osteochondroplastica (TPO) is one of the most rarely encountered tracheal diseases [20]. It is characterized by the non-malignant growth of bone and/or cartilaginous submucosal nodules that protrude into the lumen of the trachea and proximal main stem bronchi. As they arise from the tracheal cartilages, these nodules typi-

cally spare the posterior membrane, which generally helps distinguishing this diagnosis from other tracheal diseases, especially amyloidosis. This entity is likely underreported as affected patients are generally asymptomatic or have mild respiratory symptoms.

TPO affects both males and females with equal frequency, and does not appear to be influenced by smoking. Most patients are middle-aged adults though few cases have been reported in children. 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 [21]. 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 ozonae*, a bacteria 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 [20, 22, 23].

In the majority of cases the presence of TPO is identified incidentally on the basis of 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 generally minimal and self-limited. Cough, wheezing or stridor, hoarseness, 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 are frequently normal, but occasionally may 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 flow-volume loop showing 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 [22].

Chest X-rays are rarely sensitive enough to suggest the diagnosis, but may occasionally show narrowing and irregularity the of the tracheal air column with calcified deposits. 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. 6.3) [22–24]. 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.

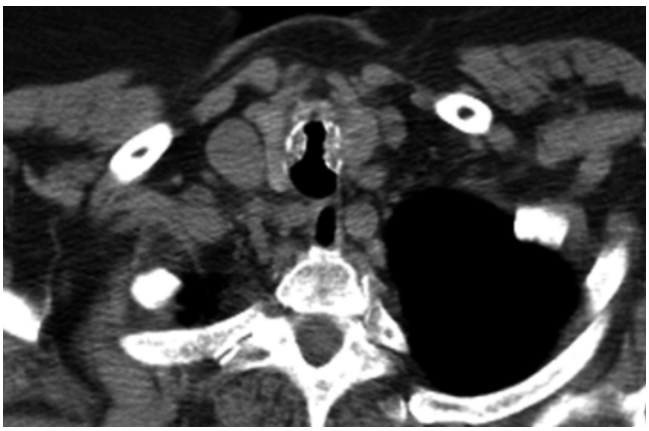

Fig. 6.3 CT scan of the chest of an 89-year-old woman with tracheobronchopathia osteochondroplastica. Partially calcified submucosal nodules are present in the tracheal walls with sparing of the posterior membranous wall

Bronchoscopy shows very characteristic lesions which can establish the diagnosis in most cases. Submucosal nodules protruding into the airway can be seen at all levels of the trachea (Fig. 6.4) but result in clinically significant narrowing (>50 %) in only a minority of patients, a threshold classically described as clinically significant based on data on tracheobronchomalacia (see below). 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 [22, 25].

Treatment of TPO is difficult, and 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 tracheal injury may result. Other techniques have been described including laser-assisted mechanical debulking. An important caveat is that any consideration of endoscopic treatment

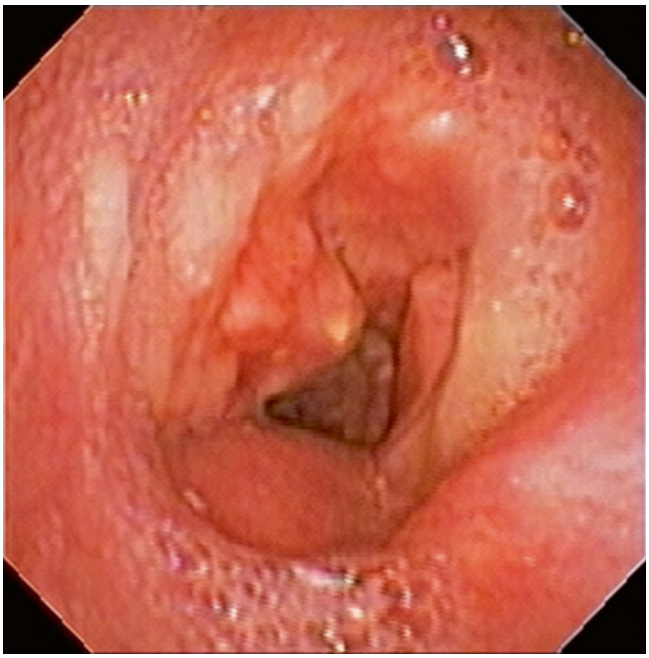

Fig. 6.4 Bronchoscopic view of tracheobronchopathia osteochondroplastica revealing osseous submucosal nodules projecting into the tracheal lumen

should be symptom-driven, as the lesions of TPO are minimally progressive in most patients and follow a benign course [22, 25, 26].

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 chronic obstructive pulmonary disease (COPD) is admitted to the pulmonary ward for his third episode of pneumonia this year. His cough has worsened and productive of purulent sputum along with increased shortness of breath. The chest X-ray reveals consolidation in the right lower lobe. Pulmonary function studies reveal severe obstruction, markedly worse than 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 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.

Tracheomalacia (from the Greek *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 airway tethered to the surrounding thoracic structures remains relatively normal during inspiration [27, 28]. 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 terminology 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 result in the same manifestations and are managed in a similar fashion, this distinction is not particularly helpful.

The vast majority of cases described in children are congenital and include mucopolysaccharidoses (such as Hurler syndrome and Hunter syndrome) and Williams-Campbell syndrome (absence of cartilages resulting in loss of structural support). Other causes of tracheomalacia in children include compression of the trachea by vascular rings or right-sided aortic arch. The persistent compression of the trachea is thought 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 airway, 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 will occur in never-smokers. 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) [27–34].

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 [27, 28]. Inflammatory cellular infiltrates may also be noted in some instances, such as in relapsing polychondritis [35].

Clinical manifestations vary based on the degree of luminal narrowing. 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. These clinical manifestations are non-specific, however, and often result in delayed diagnosis with patients incorrectly diagnosed to have chronic bronchitis or refractory asthma [27, 28].

Pulmonary function studies are typically consistent with obstruction. The severity of the obstructive syndrome is directly proportional to the degree of tracheomalacia. Obstruction that is considered out-of-proportion to the smoking history in 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 patient have been reported as well. If the extrathoracic portion of the trachea is involved, a plateau may also be noted on the inspiratory curve [27, 28, 36].

Chest X-rays are usually inadequate in the diagnosis of tracheomalacia, though they may occasionally suggest a mediastinal process that may be responsible for focal extrinsic compression and lead to additional studies. Computed tomography (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 the diagnosis of tracheomalacia is suspected, dynamic CT study should be obtained by requesting expiratory images. 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]. Multi-row detector spiral CT allow 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 ("frown sign" on CT images) (Fig. 6.5), while 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 thought 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 [27]. 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 [37, 38]. For this reason, a 75 % narrowing cutoff has been proposed by some for diagnosing tracheomalacia.

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 semi-quantitative assessment by the bronchoscopists. Bronchoscopy should be performed with conscious sedation as it allows maneuvers of cough and forced expiration not possible under general anesthesia. Morphometric bronchoscopy has been proposed as potential tool to allow quantitative analysis of air-

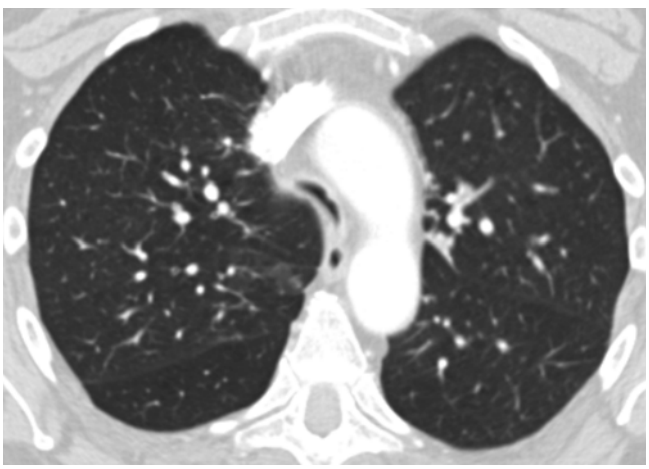

Fig. 6.5 CT scan of the chest of a 57-year-old man with severe tracheomalacia demonstrating the "frown sign"

way 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 to identify 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 of tracheomalacia should be individualized according to the type, the extent and the 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 a mediastinal mass). If possible, tracheomalacia in children should be observed as it may resolve spontaneously as the patients get older and the cartilaginous support structures mature. Non-invasive measures such as positive-pressure ventilation during sleep have been suggested, particularly in the context of excessive dynamic airway collapse, and may allow improved airflow, though the supportive evidence overall remains scarce [27, 28, 39]. Focal lesions are sometimes amenable to tracheal resection and end-to-end anastomosis, which is the 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 of mucous and occlusion of the stent. Metallic stents, while similarly efficacious in reestablishing 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 airway [40, 41]. Potential candidates for this procedure should be selected on the basis of a favorable response to silicone stenting [27]. Long-term stenting is an option for those who do respond but are not considered acceptable candidates for this invasive procedure. A recent study showed that airway stabilization via tracheoplasty or stenting for COPD-associated excessive dynamic airway collapse results in significant improvement in quality of life and physiologic parameters.

Finally, 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 infections of the lower respiratory tract and refractory asthma presents to the emergency department for the sudden onset of shortness of breath. A chest X-ray reveals a right-sided pneumothorax and chest tube thoracostomy is performed for management. A chest CT is obtained to assess for underlying parenchymal lung disease, which reveals significant bronchiectasis that predominate in the lower lobes with marked enlargement of the central airways. A bronchoscopy later confirms the diagnosis of tracheobronchomegaly. Several tracheal diverticuli are noted during the bronchoscopic examination.

Idiopathic tracheobronchomegaly, also called Mounier-Kuhn syndrome, was first reported in an adult patient in 1932. Since, over 100 cases have been reported in the literature [27]. It is considered a congenital disease affecting the trachea and proximal bronchi resulting in abnormal enlargement of the airway, leading to tracheobronchomalacia with impaired secretion clearance and recurrent infections. Though occasionally identified during childhood, the disease more often presents later in life after development of bronchiectasis and recurrent infections prompt further investigations.

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. Congenital diseases have also been reported in association with tracheobronchomegaly and include Bruton's agammaglobulinemia, Kenny-Caffey syndrome, ataxia telangiectasia and Brachmann-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. The term Mounier-Kuhn syndrome should be reserved to the idiopathic form of the disease and is also called idiopathic giant trachea. Several familial cases have been described [42–48].

Mounier-Kuhn syndrome tends to affect males with a higher frequency [46, 48]. 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 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 [49].

The pathophysiology of the Mounier-Kuhn syndrome remains to be elucidated. Histopathology data are limited, but suggest that the tracheal and bronchial walls contain 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 [50–52]. The resultant tracheobronchomalacia causes reduction of airflow, impaired secretion clearance and recurrent infections ultimately leading to bronchiectasis. Outpouchings of the tracheal mucosa, or airway diverticuli, 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 increasing further the risk of infectious complications. The prognosis of the disease varies widely, but severe cases can progress to respiratory failure.

Pulmonary function studies are typically consistent with an obstructive syndrome. 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.

Chest X-ray may occasionally suggest the diagnosis which is confirmed by the presence of central airway enlargement on chest CT (Fig. 6.6). The diagnosis is established when the airway diameter exceeds the following cutoffs, which represent 3 standard deviations above the norm, on average 2.4 cm for the right main stem bronchus, 2.3 cm for the left main stem bronchus and 3 cm for the trachea. [1, 3] The upper limits of normal for coronal and sagittal diameters in men are 25 and 27 mm respectively, and 21 ad 23 mm in women, respectively [3].

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 [53]. Despite this, a recent case series reports improvements in quality-of-life indices and physiologic parameters after both endoscopic stenting and surgical tracheobronchoplasty in patients with Mounier-Kuhn syndrome [54]. One anecdotal report described lasting improvement with low-power yttrium aluminum perovskyte laser treatment of the posterior membrane of a Mounier-Kuhn patient causing effective retraction of the tissues, though the safety of this approach remains in question [55]. Supportive interventions such as non-invasive positive-pressure ventilation at night, bronchopulmonary hygiene measures and appropriate and timely antibiotic treatment and immunizations are recommended. Few patients with Mounier-Kuhn syndrome have undergone lung transplantation and, as for cases of severe bronchiectasis, bilateral lung transplant is preferred over single-lung transplant.

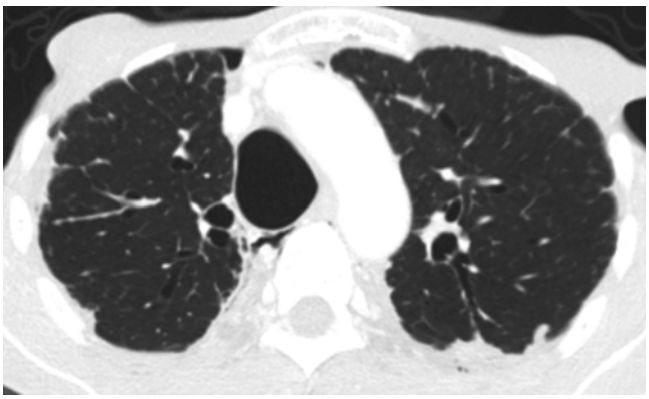

Fig. 6.6 CT scan of the chest of a 66-year-old man with tracheobronchomegaly. The antero-posterior diameter is 37 mm

Tracheobronchomegaly: Key Points

- Male predominance
- Diagnosis typically made in early adulthood
- Recurrent infections and bronchiectases 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 work-up of the respiratory symptoms. Consideration of these diseases in patients with central airway disorders is warranted as they may influence management and prognosis. While 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 (formerly Wegener's granulomatosis), 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. The physical examination reveals a saddle nose deformity and central wheezing on lung auscultation. A 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.

Relapsing polychondritis is a rare type of autoimmune connective tissue disease that affects both males and females with equal frequency. It is characterized by recurrent episodes of inflammation involving various cartilaginous structures including 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 [35, 56, 57].

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. 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 be difficult because both diseases can manifest saddle nose deformity and tracheobronchial involvement; the possible overlap between these two entities has been discussed earlier. Biopsy of the tracheal cartilage shows degeneration with fibrous changes and inflammatory cell infiltration. The histologic picture is not absolutely characteristic and specific diagnostic tests are lacking.

Central airway involvement is common in patients with relapsing polychondritis. The largest case series reported by Ernst and colleagues 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 8 patients (26 %), focal or diffuse tracheobronchomalacia in 15 patients (48 %) and focal stenosis in the remainder [58]. Other reports suggest that central airway manifestation may occur over time in approximately half of patients with relapsing polychondritis. Clinical manifestations are non-specific and include chronic cough, wheezing and/or stridor, and hoarseness in case of laryngeal involvement [56, 59].

Laboratory abnormalities are also generally non-specific 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. Antineutrophil cytoplasmic antibodies (ANCAs) have also been described in relapsing polychondritis. Since patients with active limited granulomatosis with polyangiitis have a 40 % chance to be ANCA-negative, this laboratory test does not always allow clear distinction between relapsing polychondritis and granulomatosis with polyangiitis. There is strong support for an autoimmune process directed at some extracellular components of cartilage, but no particular antibody has been identified as either sensitive or specific for the disease. Anti-type II collagen antibodies, in particular, are found in a variety of other conditions and are thought to result from a non-specific immune reaction to cartilage destruction, rather than being true pathogenic antibodies. The utility of identifying these antibodies in clinical practice is unclear [60, 61].

Pulmonary functions studies reveal findings consistent with central airway obstruction that may predominate during expiration in case of tracheobronchomalacia, or be present during both inspiration and expiration with a fixed stenosis pattern on flow-volume curve if subglottic stenosis is present. Chest X-rays are generally not helpful for the diagnosis. Chest CT reveals changes consistent with tracheobronchomalacia on dynamic images (Fig. 6.7a, 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 7 [62]. Magnetic resonance imaging has been proposed as a way to distinguish inflammation from fibrosis of the soft tissues of the central airway, but problems with resolution and prolonged image acquisition time in patients with respiratory

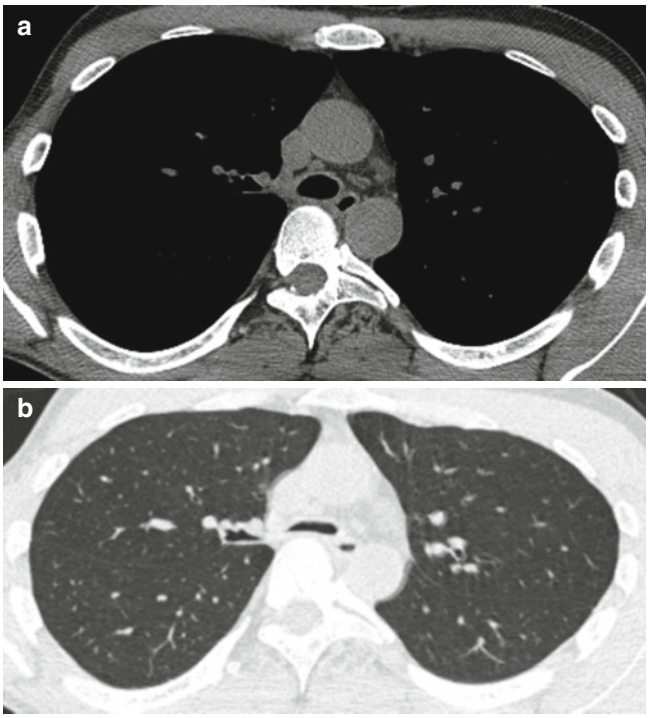

Fig. 6.7 CT scan of the chest of a 32-year-old man with relapsing polychondritis. (**a**) Inspiratory view demonstrates thickened tracheal wall with mild narrowing. (**b**) On expiration, there is collapse of the tracheal lumen

compromise limit its usefulness in clinical practice [63]. Positron emission tomography using 18F-fluorodeoxyglucose has also been suggested to assess for ongoing inflammation, but its use remains largely experimental [64].

Treatment of the underlying disease using anti-inflammatory and immunomodulating agents is warranted during periods of active inflammation. First line agents include dapsone or corticosteroids. Severe life-threatening manifestations of the disease (such as cardiac and CNS disease) should be treated with high-dose corticosteroids. Second-line agents that have been tried include cyclophosphamide, azathioprine, cyclosporine and methotrexate. In general, the evidence supporting their use is anecdotal at best. Likewise, newer biologic agents, such as the anti-TNF alpha agents infliximab and etanercept, have been used to treat refractory relapsing polychondritis and may have some efficacy on various manifestations of the disease including laryngotracheal disease. Obviously, these data are limited to case reports and small case series and represent low-level evidence [65, 66]. Supportive measure 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 ultrasonography (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 [64]. Non-invasive 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 antiinflammatory agents and airway-specific interventions, leading to better outcomes than reported in earlier studies [35, 56, 59].

Relapsing Polychondritis: Key Points

- Inflammation of cartilages, particularly ears
- Saddle nose deformity and central airway obstruction may mimic Wegener's disease
- Treatment of the underlying inflammation is warranted, when present

Granulomatosis with Polyangiitis (Wegener's)

Clinical Vignette

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

Granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis) is an autoimmune multisystem disease characterized by necrotizing granulomatous inflammation involving small to medium-sized blood vessels with vasculitis and capillaritis. The disease is characterized by the presence of anti-neutrophil cytoplasmic antibodies (ANCA) with cytoplasmic staining (or c-ANCA) directed against the PR3 antigen. PR3-ANCAs are present in 90 % of patients

with active disease, and approximately 30 % of patients with inactive disease. 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-ANCA antibodies are positive in only 60 % of those with the limited form of the disease [2, 67, 68].

Respiratory manifestations vary and include chronic rhinosinusitis, pulmonary nodules that may cavitate, diffuse alveolar hemorrhage and tracheobronchial involvement. Thromboembolic disease is also relatively common during the active phase of the disease. Tracheobronchial involvement occurs in approximately 15–55 % of patients and consists mostly of subglottic stenosis. 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 maybe be identified. Subglottic stenosis may be the only manifestation of limited GPA, and may progress relatively independently from the other manifestations of the disease. 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, 67, 68].

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

Chest CT is extremely useful in characterizing the extent and the type 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. While bronchoscopy remains the gold standard for the diagnosis of airway involvement in GPA, chest CT allows for precise quantitative analysis of the extent, type and the length of the stenosis, and helps plan appropriate endoscopic interventions.

Bronchoscopy remains the gold standard for the diagnosis of airway involvement in GPA. It is also a helpful way to 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 while non-inflammatory fibrotic stenoses are seen between exacerbations. EBUS shows circumferential thickening of the submucosa with intact bronchial cartilage. It is important to avoid aggressive endoscopic airway interventions during exacerbations as paradoxical inflammatory reactions may result in further complications [67–69].

Treatment should consist of remission-induction regimen if the disease is active, using a combination of corticosteroids and immunosuppressive agents, such as cyclophosphamide, or rituximab (anti-CD20 antibody). 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). Submucosal injections of steroids along with mechanical dilatations are often effective in providing lasting relief [70]. Mitomycin C local applications have occasionally been performed in the same setting to prevent recurrence, though the evidence supporting this practice is limited. In our practice, all subglottic stenoses are treated with a combination of submucosal injections of steroids and local applications of mitomycin C. As more distal lesions are typically related to systemic inflammation, systemic anti-inflammatory agents are preferred. Likewise, 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 after remission only [67–69].

Granulomatosis with Polyangiitis: Key Points

- May be limited (i.e. limited vasculitis) involving mostly upper airway
- Subglottic stenosis is the most common form of upper airway involvement
- Biopsies frequently non-diagnostic (consider rather 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 done during an episode of pneumonia revealed subtle infiltration of the tracheal mucosa with biopsies consistent with amyloid deposition. While the patient is now com-

pletely 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.

Amyloidosis refers to a broad and heterogeneous group of diseases caused by the abnormal extracellular accumulation of pathological insoluble serum proteins. 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 20 different serum proteins have been shown to be responsible for amyloidosis, the most common being related to light chain deposition (lymphoproliferative disorders with monoclonal gammopathy), serum amyloid A protein (chronic inflammatory conditions such as familial Mediterranean fever) and chronic renal failure (beta-2 microglobulin). Amyloidosis may be congenital or acquired, and may be limited to one organ or result in multisystem manifestations [71, 72].

Pulmonary manifestations of amyloidosis include pulmonary edema with cardiomegaly from cardiac amyloidosis, pleural effusions, interstitial lung disease with characteristic septal thickening, pulmonary nodules (amyloidomas), pulmonary hypertension, laryngeal amyloidosis and tracheobronchial amyloidosis. Tracheobronchial amyloidosis is a rare manifestation of the disease overall, and is usually considered a form of localized amyloidosis (i.e. limited to the airway), and as such associated systemic especially cardiac manifestations, are exceptionally present. It appears to predominate in males and becomes apparent in the fifth or sixth decade of life. Symptoms are non-specific 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 [73–76]. In the vast majority of cases, tracheobronchial amyloidosis is of the AL type (immunoglobulin light chains) and is limited to the respiratory tract. Local plasma cells are thought to be responsible for the deposition of amyloid fibrils in the tracheobronchial tree. The diagnosis is established on the basis of positive stain with Congo Red (bound by the amyloid fibrils), with a typical apple-green birefringence under polarized light [73, 77]. Immunohistochemistry, or better yet, laser microdissection and mass-spectrometry based proteomic analysis should be considered to confirm the nature of the protein responsible for the amyloid deposits (which, as discussed above will be an immunoglobulin light chain in the majority of cases) [78, 79]. Likewise, while generally normal, evidence of systemic amyloidosis could be investigated with cardiac studies (ECG, echocardiogram), serum and urine protein electrophoresis and immunofixation, bone marrow biopsy and renal studies (dipstick, renal function).

Pulmonary function studies may be normal in mild cases or reveal airflow obstruction, which severity is generally correlated to the degree of endoluminal involvement. The flow volume loop may reveal inspiratory ad/or expiratory plateau depending on the level of obstruction (see preceding chapters). Mixed obstructive/restrictive lung disease is possible in cases of interstitial lung disease but is uncommon, and the diffusion capacity is also usually normal.

Chest X-ray is generally not helpful for the diagnosis. Chest CT may reveal an irregular and thickened tracheal wall with occasional mass-like lesions protruding in the lumen (Fig. 6.8) [74–76]. One characteristic finding is that of tracheal and bronchial 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 18F-flurodeoxyglucose uptake on delayed images in amyloidosis [80].

Bronchoscopy is warranted to establish the diagnosis. Tracheobronchial amyloidosis is typically characterized by the presence of raised waxy yellowish or erythematous nodules that may bleed easily on contact or during biopsies. Lesions may be focal or diffusely spread. Cobblestoning of the mucosa due to submucosal amyloid deposition may also been seen. EBUS shows a thickening of the bronchial

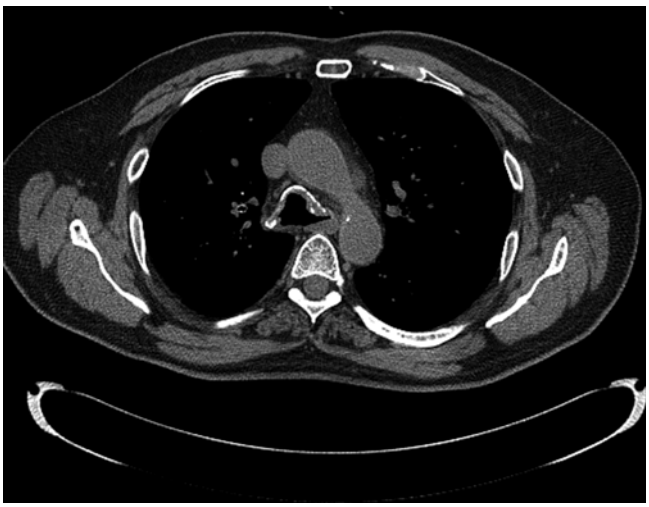

Fig. 6.8 CT scan of the chest of a 64-year-old man with tracheobronchial amyloidosis demonstrates nodular thickening of the tracheal wall with calcifications

mucosa without infiltration of the deeper tissues. EBUS can be helpful directing the site of biopsy to avoid bleeding and assisting in the choice of the more appropriate endobronchial intervention as reported for other non-malignant causes of tracheal stenosis (relapsing polychondritis, granulomatosis with polyangiitis and idiopathic subglottic stenosis).

Treatment should be individualized based on the severity of the clinical manifestations and extent of the disease. Rigid bronchoscopy is often needed in 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 extensive disease [81, 82]. As usual, supportive care should include appropriate antibiotics when needed, immunizations and bronchopulmonary hygiene measures. Prognosis varies widely with patients remaining stable over many years while others continue to deteriorate with a poor 5-year survival.

Tracheobronchial Amyloidosis: Key Points

- Usually limited to the respiratory tract (i.e. no extrapulmonary involvement)
- Congo-red stain with 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. A chest X-ray show mediastinal enlargement, unchanged when compared to previous chest X-rays. 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 a 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.

Sarcoidosis is a multisystem disease characterized by the presence of non-necrotizing granulomas in the absence of obvious etiology. Multiple organs may be affected by the disease, but the predominance of the respiratory manifestations (>90 % f the cases) suggests that an inhaled offender may trigger an exuberant type IV immune reaction responsible for the manifestations of the disease. Sarcoidosis can affect the heart, eyes, skin, peripheral and central nervous systems, joints, and kidneys. Respiratory manifestations 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, upper respiratory tract involvement, laryngeal sarcoidosis and tracheobronchial sarcoidosis [83, 84].

While bronchoscopy remains the gold standard, imaging studies may offer supportive evidence of the diagnosis. Chest–rays are rarely normal in sarcoidosis and may reveal mediastinal and/or hilar enlargement from lymphadenopathy with varying degrees of reticular or reticulonodular infiltrates, but the central airways are difficult to evaluate precisely with plain films. Chest CT can 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 apices of the lungs. Pulmonary function studies may be normal in mild cases, or may reveal various combinations of obstructive and/or restrictive defects. Central airway involvement can result in characteristic abnormalities in the flow volume curve with inspiratory and/or expiratory plateau depending on the location and extent of the tracheobronchial lesions.

Central airways appear less commonly involved than distal airways. 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. Other manifestations include hypervascularity of the mucosa, granular infiltration, plaques and polypoid lesions. While symptomatic tracheobronchial sarcoidosis is relatively uncommon, up to 60 % of patients with sarcoidosis will exhibit some type of endobronchial abnormalities, making bronchoscopy the diagnostic method of choice when sarcoidosis is suspected [84]. 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 airway may be narrowed as a consequence of extrinsic compression by enlarged mediastinal and hilar lymph nodes. A classic 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 [85]. Finally, severe cases of upper lobe fibrosis may result in airway distortion with resultant fibrostenosis and central airway obstruction [86–89].

The treatment is tailored to the severity of illness. In advanced case, systemic corticosteroids may be warranted while mild cases may be treated with inhaled steroids only. Bronchoscopic interventions can include balloon tracheo- and/or bronchoplasty, laser resection with or without stent placement [86–89]. In the case of asymptomatic disease, simple follow-up without specific treatment is generally appropriate.

Respiratory Tract Sarcoidosis: Key Points

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

Orphan Tracheopathies: Conclusions

Diseases specifically affecting the trachea are rare 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 chronic obstructive pulmonary disease. Clues hinting toward the possibility of central airway lesions include stridor or monophonic "central" wheezing and poor response to treatment. Pulmonary function studies can provide important clues, particularly when the shape of the flow volume curve is evaluated. Advances in the resolution and acquisition protocols of CT scan imaging have considerably improved the identification and characterization of these 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 when possible. The approach to diagnosis and management should include a multidisciplinary team of clinicians, radiologists, pathologists and interventional pulmonologists.

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Amyloidosis and the Respiratory Tract

7

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Introduction

Amyloidosis describes a group of diseases caused by the disruption of tissue structure and organ function resulting from accumulation of amyloid fibrils. In general, amyloid arises from the deposition of previously soluble plasma proteins within extracellular spaces in an abnormal insoluble fibrillar form. The diagnosis is often made late in the disease course, frequently as an unexpected histologic finding when a failing organ is biopsied. It may be either acquired or inherited and at least 26 different proteins can form amyloid fibrils in man [1] (Table 7.1).

It is interesting to note that given the right conditions nearly any polypeptide chain can be driven towards misfolding and aggregation but relatively few proteins are amyloidogenic *in vivo* [2]. The ultrastructural morphology and histochemical properties of all amyloid fibrils, regardless of the precursor protein type, are remarkably similar [3–5]. During amyloidogenesis, multimeric proteins dissociate to their monomeric components, and may further be enzymatically cleaved before or during their conversion into amyloid fibrils [6, 7]. There are essentially three circumstances in which amyloid deposition occurs. The first is when there is sustained abnormally high abundance of proteins that are normally present at low levels, such as serum amyloid A protein (SAA) in chronic inflammation, underlying susceptibility to AA amyloidosis. The second is when there is normal abundance of a normal, but to some extent inherently amyloidogenic protein over a very prolonged period, such as transthyretin in senile amyloidosis (ATTRwt). The third situation is the presence of an abnormal protein with markedly amyloidogenic structure, such as certain monoclonal immunoglobulin light chains in AL amyloidosis and genetic variants of transthyretin, apolipoprotein AI and fibrinogen Aα chain etc in the autosomal dominant diseases of hereditary amyloidosis.

Despite the heterogeneity of the various precursor proteins, the morphological structure and histochemical properties of all amyloid fibrils are remarkably similar. Diffraction studies of amyloid fibrils have confirmed that they all share a common core structure consisting of antiparallel β-strands lying perpendicular to the long axis of the fibril [8, 9]. 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 the pathognomonic apple green birefringence when viewed under cross 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 [10] reflects its specific binding to an, as yet, uncharacterised ligand common to all amyloid fibrils which forms the basis for diagnostic scintigraphic imaging of amyloid with radiolablelled-SAP [11].

The clinical phenotype of amyloid deposition is remarkably diverse, ranging from an asymptomatic small, localised deposit to a systemic, rapidly lethal multisystem disease [12]. Almost any organ can succumb to the effects of fibril deposition including the lung and in most instances the disease presents with multi-organ involvement. While amyloid deposits may be widespread clinically important amyloidosis results

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Table 7.1 Classification of the systemic amyloidoses

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
$A\beta_2M$	β_2-microglobulin	Periarticular and, occasionally, systemic amyloidosis associated with long-term dialysis
ATTR	Normal plasma transthyretin	Senile systemic amyloidosis with prominent cardiac involvement
ATTR	Genetically variant transthyretin	Autosomal dominant systemic amyloidosis Familial amyloid polyneuropathy
ACys	Genetically variant cystatin C	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
AFib	Genetically variant fibrinogen A alpha chain	Autosomal dominant systemic amyloidosis Non-neuropathic with prominent renal involvement
ALect 2	Leukocyte chemotactic factor 2	Slowly progressive renal amyloid with nephrotic syndrome and liver involvement

from the disruption of the structure, integrity and function of affected tissues and organs. The natural history of amyloidosis is usually of progressive accumulation. Although there is continual low-grade turnover of amyloid deposits, clinical progression reflects the fact that the fibrils are being laid down faster than they are cleared away. Amyloid deposits can therefore regress if the balance is tipped in favour of clearance. As such, many of the currently available treatment strategies have focussed on reducing the supply of fibrils by halting the production of the culpable plasma protein. The primary goal of therapy is thus to prevent further progressive amyloid deposition. Although most types of amyloidosis are progressive and unremitting, there are numerous reports describing actual regression of amyloid when the underlying inflammatory or other condition have been successfully treated [13–19]. Current efforts are being directed at developing treatment strategies which may result in more pronounced disappearance of the amyloid fibrils although human trials have not yet been completed in this regard [20].

Diagnosis and Evaluation of Amyloidosis

As amyloidosis is a remarkably heterogenous disease it may present to a variety of different medical specialties. There are numerous reasons for patients with amyloidosis to present to the respiratory physician. Chronic pulmonary conditions can themselves give rise to systemic amyloidosis, most commonly of AA sub-type. While these patients rarely present with symptomatic involvement of the lung 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 amyloidosis itself whereby amyloid deposits are found in the lung 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 be detected incidentally on chest radiography or biopsy. Lastly, it is important to recognize that, especially in the context of AL amyloidosis, pulmonary complications may also arise from treatment.

The key first step in diagnosis is obtaining tissue evidence of amyloid fibril deposition. The diagnostic gold-standard for the presence of amyloid is histological confirmation by Congo red staining, producing red-green birefringence under crossed polarised light [3] (Fig. 7.1a, c). Most tissue specimens, ranging from needle biopsies to open surgical resections, can be studied although small biopsies are open to sampling error given the often focal nature of the deposits. Standard formalin fixation of the biopsy specimen is appropriate in the majority of cases. Samples can then be embedded in paraffin for cutting. These samples are suitable for the Congo red stain as well as subsequent immunofixation. It is also appropriate for laser capture microdisection and mass spectrometry described later in the chapter. Biopsy of any organ can be hazardous in amyloidosis as there is an increased risk of haemorrhage. Significant bleeds having been reported in 5 % of liver biopsies [21], although more recent data from renal biopsies is reassuring [22]. A case report from 1987 described fatal lung haemorrhage following transbronchial biopsy in a patient with amyloidosis. The post mortem findings showed the biopsied blood vessels infiltrated with amyloid [23]. A further case series by Utz et al. published in 1996 reported no major complications in 11 patients following transbronchial lung

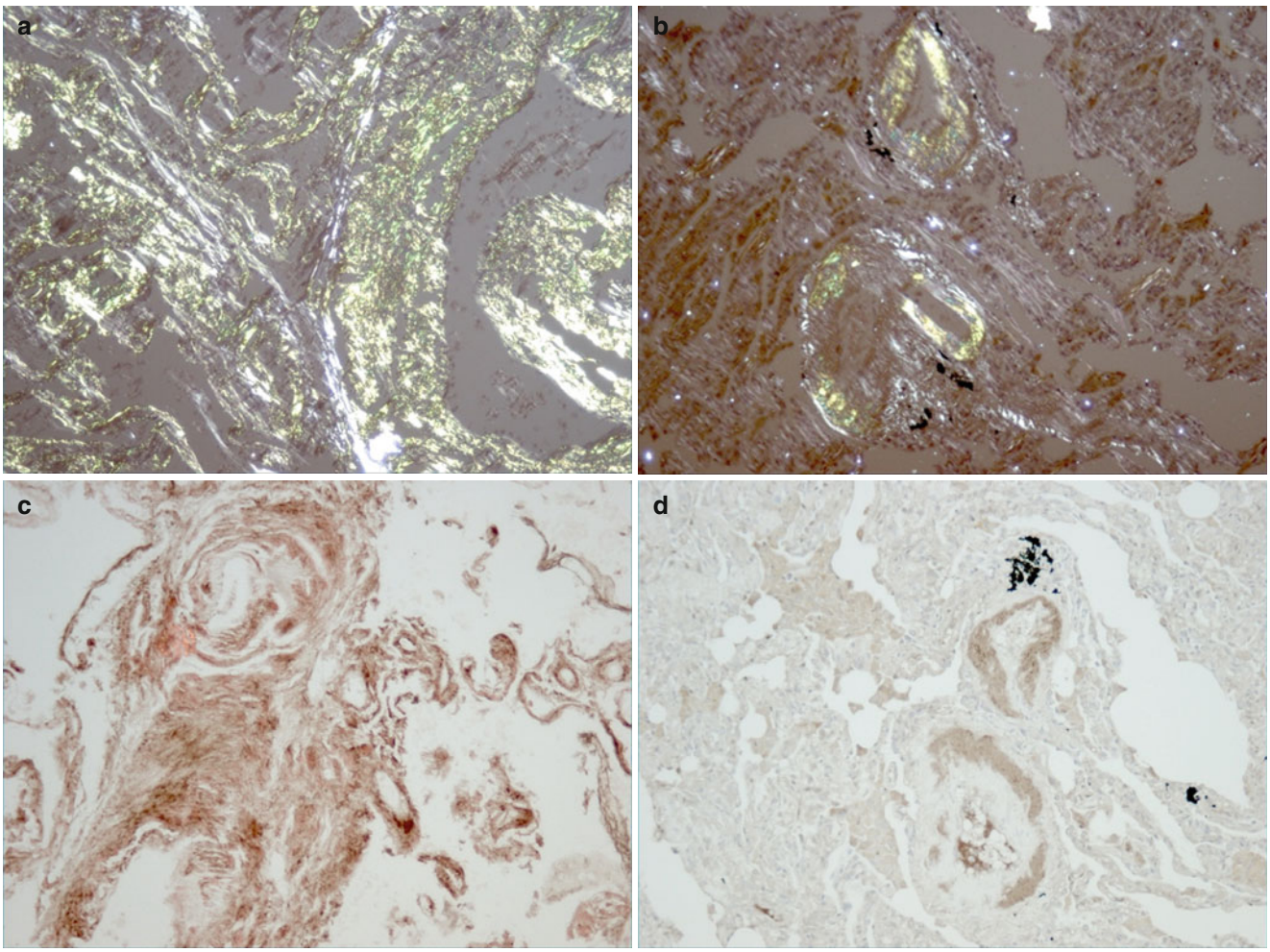

Fig. 7.1 Tissue confirmation of amyloid subtypes. Lung biopsies showing characteristic histological appearance of amorphous amyloid deposits stained with Congo red from patients with lambda light chain restricted AL amyloid (**a**) and ATTRwt amyloid (**b**). Confirmatory testing is shown by immunohistochemistry using anti-lambda light chain antibodies (**c**) and anti-transthyretin antibodies (**d**)

biopsies however 2 of the 11 cases were reported to have 100 mL blood loss [24]. A less invasive alternative in suspected disease is fine needle aspiration and this has been used successfully in the respiratory tract [25, 26]. The increased risk of haemorrhage in amyloidosis is multifactorial. There is often increased fragility in involved blood vessels as well as reduced elasticity of amyloidotic tissues. Very occasionally in AL type amyloid an acquired deficiency of clotting factors IX or X is seen [27–29]. Interestingly the factor deficiencies are most often due to sequestering of the circulating factor in the liver and spleen. It is not generally due to deficient factor production or the development of an inhibitor as is sometimes seen in other clonal lymphoproliferative disorders.

Once amyloid is identified immunohistochemical stains are then used to determine the fibril protein type as this ultimately guides further therapeutic interventions (Fig. 7.1b, d) [30]. Suitable antibodies for most of the common amyloid subtypes are widely available. This includes antibodies to kappa and lambda light chains, SAA and transthyretin. It should be noted that although immunohistochemistry is usually definitive in AA amyloidosis, it is non-diagnostic in about 20 % of AL deposits [31, 32]. Expertise in the immunohistochemical typing of hereditary amyloid is restricted, and definitive immunohistochemical typing of amyloid deposits cannot always be achieved [33]. Laser capture micro-dissection and mass spectrometry is fast being established as the new gold-standard in fibril typing. The technique involves micro-dissection of a suspected amyloid deposit, identified by positive Congo red staining, from a cut specimen on a microscope slide. The microscopic protein deposit is removed from the slide and then analyzed by mass spectrometry to identify the fibril sub-type, this technique is successful in the vast majority of cases. It is especially useful in those patients who cannot be confidently diagnosed through immunohistochemical typing however the technique is currently limited by availability [34]. If Congo red positivity is not demonstrated but the clinical suspicion of a clonal lymphoproliferative disorder being the source of the symptoms is still high one should consider Nonamyloidotic Monoclonal Immunoglobulin Deposition Disease (NMIDD). This may be due to either heavy chain or light chain deposition within the tissues but without amyloid fibril formation. This is a rare

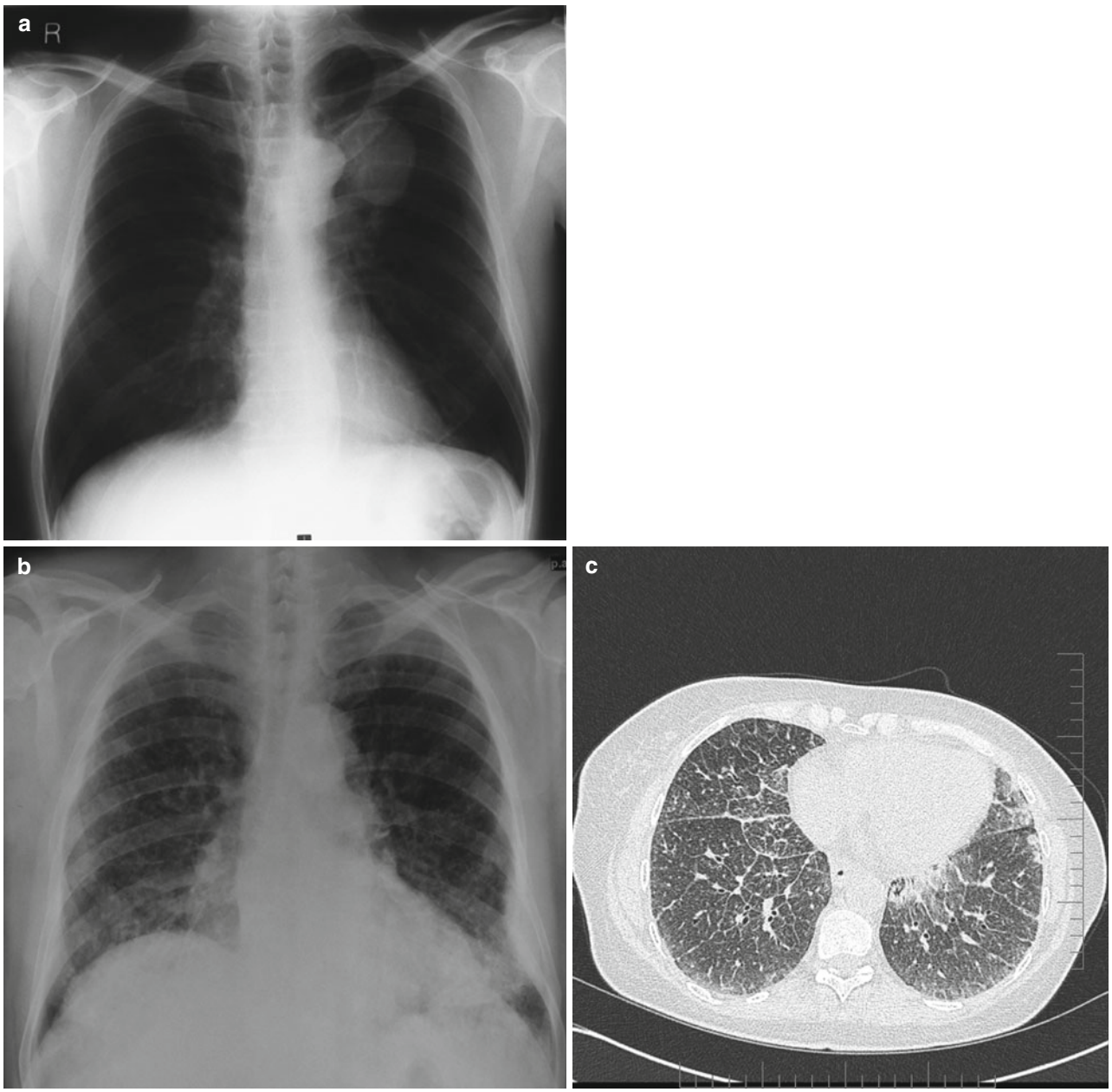

Fig. 7.2 Radiologic appearance of amyloid deposition. Chest x-ray showing isolated pulmonary amyloidoma (**a**). Chest X-ray demonstrating the typical intersitioal pattern associated with parenchymal amyloid fibril deposition (**b**). High resolution CT of the chest on the same patient confirming intersitioal infiltration (**c**)

entity but the presentation can be very similar to more typical AL amyloid of the lung. The diagnosis is again dependent on tissue biopsy often requiring special pathology expertise. Clinically, management is very similar to that of AL amyloid given that the underlying etiology is a clonal disorder.

If a genetic variant is suspected one should pursue more detailed analyses examining for mutations in the gene giving rise to the amyloidogenic fibril. In general sequencing is the preferred modality and ideally samples should be sent to a reference lab with expertise in this area. A web-based repository reviewing all currently known mutations in genes with amyloidogenic potential has been recently made available to help guide these investigations (http://amyloidosismutations.com).

Once histological confirmation of amyloid has been obtained the extent of the organ deposition and dysfunction needs to be established. In respiratory tract amyloidosis this can be challenging and the optimum imaging technique can vary depending upon the distribution of deposits. In many cases however, it may be normal. Plain radiography as an initial assessment can be helpful with findings ranging from local amyloidomas presenting as intrathoracic mass lesions (Fig. 7.2a), to non-specific reticular interstitial infiltrates

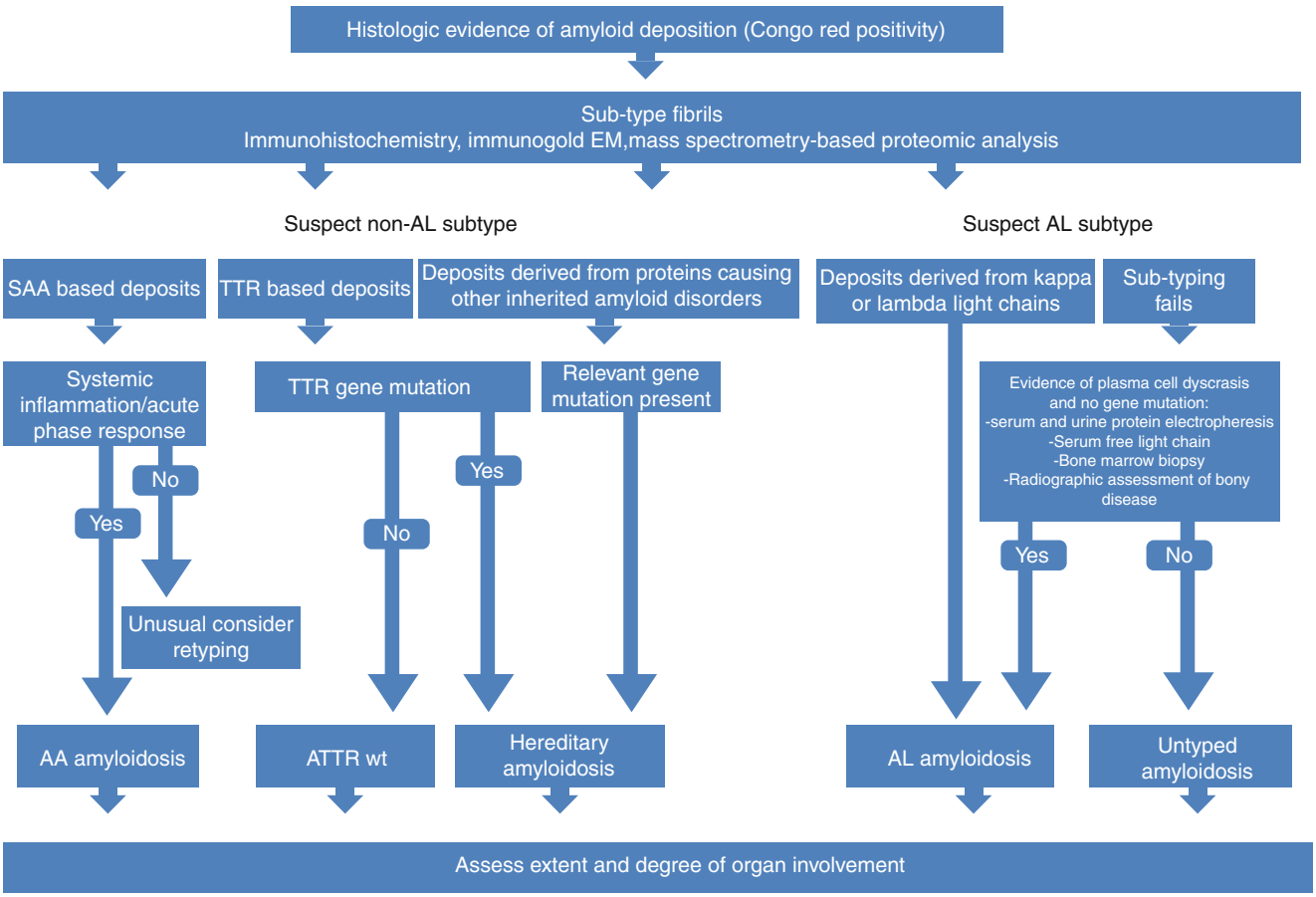

Fig. 7.3 Algorithm for investigations of patients with suspected amyloidosis

(Fig. 7.2b). Computed tomography (CT) scanning is particularly useful in further defining interstitial disease (Fig. 7.2c). In combination with positron emission tomography (PET) imaging it can also help to better define the metabolic activity of a solid lesion thus aiding differentiation from more typical intrathoracic malignancy or metastases as well as rare entities such as plasmacytomas [35]. 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 disease and are useful in guiding therapeutic decisions. Evidence of extra-pulmonary systemic disease should be sought clinically and by performing relevant serologic and radiographic investigations. A diagnostic algorithm is presented in Fig. 7.3.

If AL amyloid is suspected it is important to identify the underlying clonal disease process. The plasma cell clones that underlie systemic AL amyloidosis are often subtle and may not be detected by bone marrow examination or immunofixation of serum and urine. In recent years, the use of the serum free light chain assay has increased the diagnostic sensitivity in testing for clonal disease [36, 37]. Immunoglobulin gene rearrangement studies may identify subtle clones in either the bone marrow or, in the case of localised AL, within the amyloidotic tissue itself [38]. A number of other non-invasive techniques are available to assess the overall amyloid burden. Radiolabelled ^{123}I-human SAP localises specifically to amyloid deposits *in vivo* in proportion to the quantity of amyloid present and thereby enables diagnosis, quantification and monitoring of amyloid [11]. SAP scintigraphy is useful in visualising amyloid in the major organs of the abdomen (Fig. 7.4a). Localisation to the lungs is poor thus it is not routinely used for identifying or monitoring amyloid deposits in the respiratory tract however dense fibril deposits as seen in large amyloidomas may occasionally show distinct tracer uptake (Fig. 7.4b). In combination with single photon emission computed tomography (SPECT)-CT imaging SAP uptake can be better delineated; better characterizing the degree of uptake within an organ or lesion (Fig. 7.4c). It is also important to note that while it is a very specific test for the presence of amyloid, alone it cannot reliably differentiate the fibril sub-type. Cardiac amyloidosis is best evaluated by a combination of echocardiography and ECG [39–41]. Two-dimensional Doppler echocardiography classically reveals concentric

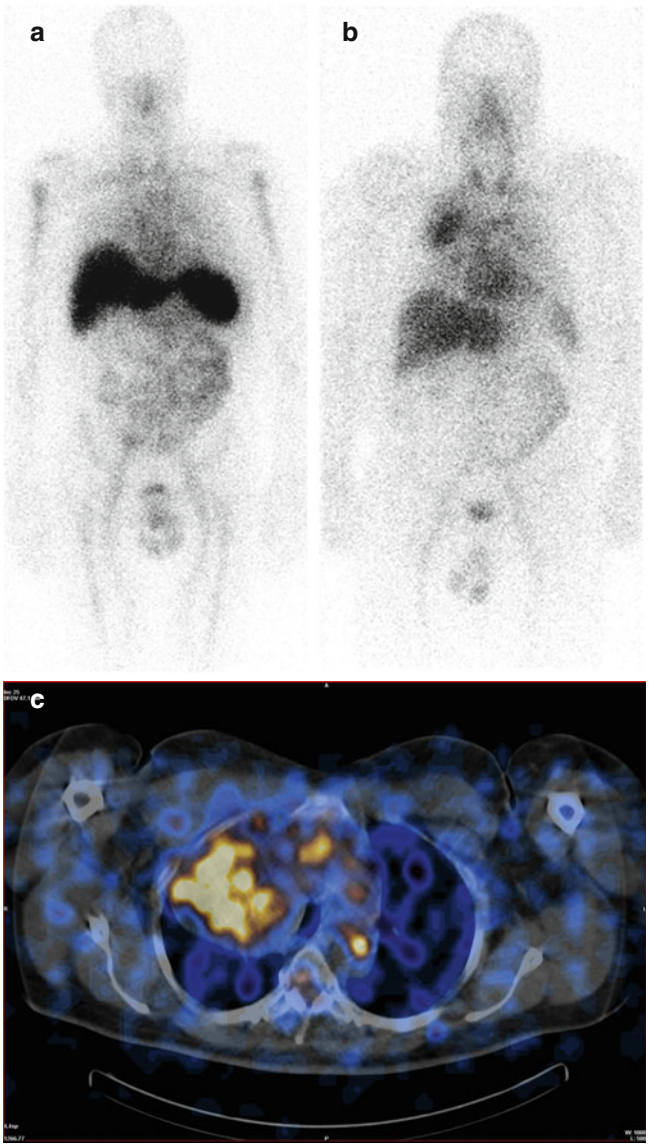

Fig. 7.4 Scintigraphic assessments using ^{123}I-human SAP. An anterior whole body scintigraphic image from a patient obtained following intravenous injection of ^{123}I-human SAP showing abnormal uptake into the amyloid deposits within the spleen, liver and bone marrow (**a**). An anterior plasmacytoma 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**)

biventricular wall thickening with a restrictive filling pattern [42]. Amyloid primarily causes diastolic dysfunction with a decline in the ejection fraction occurring generally in the latter stage of the disease [40]. The ECG may be normal but in advanced disease commonly shows small voltages, pathological 'Q' waves (pseudo-infarct pattern) in the anterior chest leads and conduction abnormalities. Cardiac magnetic resonance imaging (CMR) is being used more frequently and is extremely useful in identifying cardiac amyloid. Typical appearances are of homogenous late gadolinium enhancement [43]. ^{99m}Tc-3, 3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy is fast becoming a powerful imaging tool in the investigation of cardiac amyloid. It is a specific test indicative of fibril deposition within the heart with newly emerging data suggesting that the degree of uptake and pattern of distribution in the extra-cardiac soft tissue may even be specific for ATTR amyloid [44–46]. If these studies are confirmed prospectively then this may evolve as a tool whereby a non-invasive diagnostic test can be used to confirm fibril sub-type. Elevation of N terminal Pro brain naturetic peptide (NT-Pro BNP) and cardiac troponins can also be helpful in establishing whether a patient has cardiac amyloid. Together they have become key markers to risk stratify patients and guide therapy [47]. It is important to recognize that these enzymes are not always specific and can be elevated for many reasons such as renal impairment and other forms of cardiomyopathy; however a normal NT-Pro BNP can often exclude clinically significant cardiac involvement [48, 49].

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. The list of chronic inflammatory, infective or neoplastic disorders that can underlie it is almost without limit (Table 7.2). Biopsy and post-mortem series suggest that the prevalence of AA amyloid deposition in patients with chronic inflammatory diseases is between 3.6 and 17 %, though a smaller proportion of patients have clinically significant amyloidosis [50, 51]. The amyloid fibrils are derived from cleavage fragments of the circulating acute phase reactant, SAA [52]. SAA is an apolipoprotein of high density lipoprotein (HDL) [53], which is synthesised by hepatocytes under the transcriptional regulation of cytokines including IL-6, IL-1 and TNF-α [54]. In health the circulating concentration of SAA is around 3 mg/L, but this can rise by more than a thousand fold in the presence of inflammation. The circulating concentration of SAA tends to parallel 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 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 disease can develop very rapidly, the median latency between presentation with a chronic inflammatory disorder and clinically significant amyloidosis is almost two decades [55].

Table 7.2 Conditions with Respiratory Manifestations associated with systemic AA amyloidosis

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

The most common respiratory disease underlying AA amyloidosis in the United Kingdom is bronchiectasis. It is the fifth commonest cause, 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 22.2 years, with a wide range ± 12.2 years. The mean age at presentation was 50.6 ± 13.5 years. Eight cases (50 %) had cystic bronchiectasis, four of whom died from suppurative pulmonary infections. The other eight patients had chronic fibrotic changes, four of these eight cases were considered to be the sequelae of previous TB infections [56]. It is important to recognize however that the prevalence of bronchiectasis is falling due to both earlier treatment of necrotizing pneumonia and prevention of pulmonary infections via routine immunization programmes.

Neoplasia including primary lung malignancies, lymphoma, adenocarcinoma and polyclonal lymphoid diseases like Castlemans disease account for approximately 3 % of AA amyloid cases [57–61]. Castleman's disease (angiofollicular lymph node hyperplasia) is a rare B cell lymphoproliferative disorder characterized by giant hyperplastic lymph node follicles, capillary proliferation and plasma cell infiltration [62, 63]. It is often associated with a significant systemic inflammation and marked constitutional symptoms. It comprises solitary and multicentric forms, and there are hyaline vascular and plasma cell variants histologically [64]. Multicentric disease, commonly of the plasma cell type, usually has an aggressive and rapidly fatal course. It is most often seen in the context of HIV infection and thought to be related to human-herpes virus 8 infection with the disease driven by either host or virus derived IL-6. In Asia there is also a well described entity of multicentric Castleman's not associated with HHV-8 but still driven by cytokine overproduction [63]. Unicentric disease tends to occur in younger patients and is of the hyaline vascular type in more than 70 % of cases, and of plasma cell type or mixed histology in the remainder [65]. 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 recognized rare complication of all forms of angiofollicular lymph node hyperplasia, and is usually of systemic AA type occurring as a result of the persistent cytokine-driven acute phase response [58]. Surgical resection of unicentric tumours can result in complete remission and excellent long term outcome [58, 66]. Chemotherapy, anti-IL6 immunotherapy and anti-virals have also been explored in the treatment of this condition, tocilizumab (humanized monoclonal anti-IL6 receptor antibody) is now established as the treatment of choice in this disease [67–69]. While in Castleman's disease IL-6 seems to be the primary driving factor of systemic inflammation in other lymphomas the exact pathophysiology driving the systemic inflammatory response is not well understood. However, it is again hypothesized that tumour derived cytokines are produced which stimulate the synthesis of serum amyloid A protein by the liver [70].

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 the commonest single disease resulting in AA amyloid. This remains the case in many parts of the developing world and is likely to be vastly underreported. Other less common underlying conditions include cystic fibrosis, sarcoidosis and Kartagener syndrome.

In general, AA amyloidosis is a systemic condition that results in organ dysfunction due to widespread deposition of AA amyloid fibrils. The primary and often the first organ involved is the kidney, usually presenting with proteinuria. Progressive renal dysfunction follows often accompanied by overt nephrotic syndrome. Splenic amyloid deposits are almost universally present and are detectable by SAP scintigraphy. This is often of little clinical significance and patients are usually entirely asymptomatic with the amyloidotic spleen frequently not palpable. Hepatic involvement and autonomic neuropathy are well recognised but usually occur only very late in the disease. Cardiac AA amyloidosis is extremely rare occurring in less than 2 % of cases often as a

late finding. Overt respiratory tract involvement has not been a clinical feature among over 400 patients with systemic AA amyloidosis evaluated in our own unit. In systemic amyloidosis it is not uncommon to see small deposits of amyloid in the blood vessels of most tissues including the lungs, however these deposits are usually asymptomatic and regarded as incidental. Although there have been a few reports of systemic AA amyloidosis affecting the lungs, fibril typing was generally imperfect [71]. All studies in which the fibril protein has actually been sequenced identified AL type. As emphasized previously diagnosis of amyloid relies on a high index of clinical suspicion and requires histological confirmation.

SAP scintigraphy provides a useful non-invasive method of diagnosis at the UK National Amyloidosis Centre. When considering AA amyloid it can be used as a screening examination with greater than 98 % accuracy as the vast majority of these patients will have at least splenic uptake [55]. That said the most effective form of basic screening in medical or respiratory practice is to target patients at risk of developing AA amyloidosis, identifying those with ongoing poorly controlled inflammation and to performing urinalysis at each clinic attendance. More than 95 % of patients with AA amyloidosis will have significant proteinuria on dipstick testing which should prompt further specialist investigation [55]. The prognosis of AA amyloidosis depends on the degree of renal dysfunction at presentation, the chronicity of the inflammatory process and whether the underlying chronic inflammatory disease can be effectively suppressed, so that the plasma SAA is maintained below 10 mg/l. When the supply of fibril precursor protein is substantially reduced by such methods, AA amyloid deposits frequently regress and renal function can improve [55, 72]. If the acute phase response continues unabated, 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 (as in cystic fibrosis or Kartagener syndrome) 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 that of age matched non-diabetic patients on the end stage program 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. Nephrotic syndrome is a major risk factor for sepsis, particularly in patients who are predisposed to infection such as those with bronchiectasis. A minority of patients go on to receive renal transplants. The published outcomes are rather variable but our series of almost 40 highly selected patients had excellent outcomes with an 82 % 5-year graft survival [73]. It is recommended in patients with AA amyloidosis that renal transplantation is considered in those who have excellent control of their SAA levels and regular monthly monitoring is recommended to ascertain suitability. Unfortunately patients with underlying respiratory conditions causing AA amyloidosis may be unable to have renal transplants as unresolved bacterial infections and incurable malignant disease remain contraindications.

Systemic AL Amyloidosis

Systemic AL amyloidosis is the commonest type of systemic amyloidosis accounting for approximately 60 % of cases. It may occur in association with any form of monoclonal B cell dyscrasia [74, 75]. The precursor proteins are monoclonal immunoglobulin light chains and generally consist of the whole or part of the variable (V_L) domain [76, 77].

A number of conditions localised to the thoracic cavity can underlie systemic AL amyloidosis. Although rare, an isolated plasmacytoma can secrete enough monoclonal free immunoglobulin light chains into the circulation to produce systemic AL amyloid deposits [78]. Rarely, this can present as a chest mass (Fig. 7.4b, c). While more commonly associated with AA amyloid, Castleman's tumours, both unicentric and multicentric, can be associated with monoclonal immunoglobulin light chain production and are a rare cause of AL amyloidosis [79]. The commonest condition managed by respiratory physicians which can cause both systemic and respiratory localised AL amyloid deposits is Sjogren's syndrome which is discussed later in the chapter.

Systemic AL amyloidosis is most commonly associated with a clonal proliferation of plasma cells. A degree of amyloid deposition is seen in up to 15 % of patients with overt myeloma, but the vast majority of patients (more than 80 %) who present with clinically significant AL amyloidosis have a low grade plasma cell dyscrasia [80]. AL amyloidosis usually presents in patients over the age of 50 years, although it can present in very young adults [80]. Clinical manifestations are extremely variable since almost any organ other than the brain can be directly involved [81]. Although certain clinical features are strongly suggestive of AL amyloidosis (Table 7.3) and multi-organ dysfunction is common, many patients initially present with non-specific symptoms such as malaise and weight loss. The outlook of untreated AL amyloid is far worse than AA type, with a 5 year survival of approximately 10 % and a 10 year survival of less than 5 % [80]. Most affected individuals eventually die of heart failure, uraemia or autonomic failure. Criteria have been

Table 7.3 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
Pulmonary	Shortness of breath; Restrictive or obstructive defects; decreased diffusion capacity
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
Lymphoretiicular	Splenomegaly; Lymphadenopathy
Adrenal axis	Hypoadrenalism (rare)

Table 7.4 Criteria defining organ involvement with in AL amyloidosis

Organ	Defining criteria
Kidney	24-h urine protein >0.5 g/day, predominantly albumin
Heart	Echo: mean wall thickness >12 mm, no other cardiac cause
Liver	Total liver span >15 cm in the absence of heart failure or alkaline phosphatise >1.5 times institutional upper limit of normal
Nerve	Peripheral: clinical; symmetric lower extremity sensorimotor peripheral neuropathy
	Autonomic: gastric-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration
Gastrointestinal tract	Direct biopsy verification with symptoms
Lung	Direct biopsy verification with symptoms
	Interstitial radiographic pattern
Soft tissue	Tongue enlargement
	Arthropathy
	Claudication (presumed vascular amyloid)
	Skin lesions
	Myopathy (by biopsy or pseudohypertrophy)
	Lymph node (may be localized)
	Carpal tunnel syndrome

Adapted from the 2005 criteria [169]

published to formally document involvement of the major organ systems include the lung in AL amyloidosis (Table 7.4).

The breadth of symptoms associated with pulmonary involvement can be either directly related to respiratory tract amyloid deposits or due to sequelae from extra-pulmonary organ dysfunction. Although microscopic deposits of amyloid are almost universally present in the lungs, in the vast majority of cases dyspnoea is secondary to cardiac involvement. A restrictive cardiomyopathy is found in up to one third of all patients with AL amyloid, ultimately being the cause of death in one half [82]. Renal involvement is also frequent in AL amyloidosis and presents in the same manner as renal AA amyloid [83]. Gut involvement can cause motility disturbances (often secondary to autonomic neuropathy), malabsorption, perforation, haemorrhage, or obstruction [84]. Peripheral neuropathy occurs in one fifth of cases and typically presents with a painful sensory polyneuropathy followed later by motor deficits [80]. Autonomic neuropathy causing orthostatic hypotension, impotence, and gastrointestinal disturbances may occur in isolation or with a peripheral neuropathy [81].

As previously stated the chest radiograph is usually normal in systemic AL amyloidosis. Nodular "amyloidomas" arising from a small local population of clonal plasma cells secreting amyloidogeninc light chain may be detected appearing as focal masses. A diffuse reticulonodular pattern may also be present if the lung parenchyma is involved. Lung function tests sometimes show a restrictive pattern and rarely reduced gas transfer due to extensive alveolar deposits [85]. Persistent pleural effusions have been described in 5.5 % of patients yet this is more commonly associated with amyloid heart disease [86]. Nephrotic syndrome secondary to renal amyloid deposits can also result in gross salt and water overload and often, in combination with cardiac involvement, can result in pulmonary oedema and pleural effusions. Amyloid deposits can occasionally directly involve

the pleura causing disruption of normal pleural function and resultant effusions. Chronic pleural effusions secondary to pleural amyloid are often refractory to management with diuretics and require recurrent drainage or pleurodesis [86].

Amyloid Deposits in the Respiratory Tract

First described by Lesser in 1877, localised amyloidosis of the respiratory tract ranges from asymptomatic pulmonary nodules to diffuse parenchymal deposits. Presenting symptoms can mimic a variety of lung pathology and depends on the location of the amyloid fibrils. Initial investigations with routine imaging can be unhelpful in confirming the diagnosis. A number of classifications have been proposed based upon radiographic or bronchoscopic findings but have not been widely adopted [24, 87]. In general amyloidosis is best classified by the fibril protein (Table 7.1), and then by the sites of clinical involvement.

Localised amyloid deposition is not uncommon although often goes undiagnosed. It results either from local production of fibril precursors [88, 89], or from properties inherent to the particular microenvironment, which favour fibril formation from a widely distributed precursor protein [90]. The vast majority of localised amyloid deposits are of AL type [91, 92] with symptomatic deposits occurring most frequently in the eye [93], skin [94], respiratory [24, 95] or urogenital tracts [96, 97]. They are often associated with extremely subtle focal monoclonal B cell proliferation confined to the affected site. Surgical resection of these localised 'amyloidomas' can sometimes be curative if the underlying clonal are removed [97]. Symptomatic apparently localised amyloid deposits can rarely be manifestations of systemic disease and patients should always be fully investigated to exclude more generalised amyloid deposition [30].

Thorough evaluation of respiratory tract amyloidosis and biopsy confirmation is required to determine the need for treatment and the most suitable modality based on fibril subtype. However, 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 [98]. It represents 0.5–1 % of benign laryngeal disease, its incidence increases with age but it occasionally affects young adults [99]. Discrete nodular and diffuse infiltrative types of laryngeal amyloid were initially described in 1949 [100], the diffuse pattern with an intact mucosa being more common, sometimes with tracheobronchial extension [92]. The macroscopic appearance is often seen as diffuse subepithelial oedema without mucosa or nodular alterations [101]. The amyloid deposits occur most commonly in the ventricles followed by the subglottis, the aryepiglottic folds and the true vocal cords [92]. Presentation is usually with hoarseness or rarely stridor, but can cause a sensation of 'fullness' in the throat, choking, and dyspnoea on exertion [102]. The aetiology remains unclear, there is no reported association with alcohol use, smoking, vocal abuse or infections [98]. One proposed explanation for the predilection of the larynx is that the production of light chains may be arising from B-cell clones within mucosal associated lymphoid tissue [95, 103]. Deposits are predominantly lambda in origin [96, 104].

The diagnosis is usually made following larnygoscopy and biopsy. The extent of infiltration is best determined with MRI examining specifically for tracheobronchial extension. On MRI imaging laryngeal amyloid is reported to give intermittent T1-weighted signal intensity and low T2-weighted signal intensity similar to skeletal muscle. It is felt to be superior to CT images when evaluating amyloid of the pharynx, larynx and trachea [105]. Systemic amyloidosis should be excluded and investigations for an underlying plasma cell dyscrasia are imperative. There are case reports of extramedullary plasmacytoma with amyloid deposition affecting the larynx and it is important to distinguish this from a localised deposit of amyloid as this clearly changes the prognosis and approach to management [106].

Very rarely apparently localised laryngeal amyloid deposits can be due to a feature of hereditary systemic apolipoprotein AI amyloidosis (AApoAI). Apolipoprotein AI is a major constituent of high density lipoprotein (HDL) [107]. Wild type apolipoprotein AI is amyloidogenic and is present as traces of amyloid in human aortic atherosclerotic plaques in 10–20 % of autopsies although rarely leads to overtly symptomatic disease [108]. Fourteen separate apolipoprotein variants have been reported to cause this [33, 89, 109, 110] and in three of these, the major site of organ damage is the heart. Numerous other amyloidogenic variants have been reported and are associated with specific genetic alterations and a different pattern of organ distribution. Depending on the mutation, patients can present with massive abdominal visceral amyloid involvement [111], predominant cardiomyopathy [109] or a familial amyloid polyneuropathy like syndrome [112]. Laryngeal and cutaneous deposits producing hoarseness, infiltrative plaques, and petechial rashes are associated with the apolipoprotein AI Arg173Pro, Ala175Pro, Leu90Pro, and Leu178His variants. Case reports suggest that the macroscopic appearances of the laryngeal deposits in AApoAI amyloidosis are different from those seen in localised AL disease, they appear as small irregular floppy proliferations affecting the borders of the vocal folds in contrast to firm bulky deposits in the localised AL form [113].

AApo AI amyloid is autosomal dominantly inherited with variable penetrance and a family history of the disease may therefore be lacking. Performing immunohistochemistry on biopsy specimens for both AL kappa and lambda and apolipoprotein AI is recommended. Genetic sequencing looking for Apo AI mutations 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 segmental bronchi and frequent involvement of the submucosal vessels [24, 114]. A literature review from 1983 identified 67 cases of which 57 were diffusely infiltrative (multifocal submucosal plaques) and the remainder were nodular or 'tumour-like' [87].

Presenting symptoms include dyspnoea, persistent cough and haemoptysis [115]. Narrowing of airways can cause an obstructive airflow defect and cases of tracheobronchial amyloidosis simulating asthma have been reported. Deposits may also cause distal atelectasis, recurrent pneumonia or lobar collapse and solitary nodules may be mistaken for endobronchial neoplasia [116]. Routine chest x-ray may be misleading. In a recent review of 64 cases, 70 % of cases had normal radiographic findings [117]. Imaging with computed tomography (CT) commonly shows tracheobronchial thickening, stenosis, atelectasis and patchy shadows with no specific findings attributable to amyloid deposition. 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 skeletal muscle [105]. Dual phase FDG PET/CT imaging can be used to differentiate between malignancy and amyloid deposits. Early phase FDG metabolic activity can be seen but delayed images show reduced activity which would not be seen with malignancy [118]. Given the non-specific nature of the imaging of tracheobronchial amyloidosis the diagnosis is often delayed as it most often requires bronchoscopy and biopsy [119]. Tracheobronchopathia osteoplastica, characterised by calcified or cartilaginous submucosal nodules within the airways [120–122] and relapsing polychondritis are the principle differential diagnoses [123, 124]. Ding et al. reviewed the literature in 2010 and reported the natural history of 64 cases. The median age at diagnosis was 49 (range 21–82) years. The median time to diagnosis was 37 months, with a male to female ratio of 1.21 [117]. Although symptomatic tracheobronchial amyloidosis is usually localised, its course is not always benign and overall survival is only 31–43 % at 4–6 years: three of seven cases followed up by Hui died of respiratory failure or secondary pneumonia [125], and three of four Mayo Clinic patients died within 79 months of diagnosis [24].

Parenchymal Pulmonary Amyloidosis

Amyloid within the lung parenchymal tissue is the most frequently detected respiratory manifestation of amyloidosis [126]. It can be divided radiographically into solitary/multiple nodules or a diffuse alveolar-septal pattern [127, 128].

Nodular pulmonary amyloidosis is almost always due to localised AL deposits and is usually an incidental finding on chest radiography. Although the lesions may appear 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 malignancy. A recent case report however, suggests that PET imaging can give false positive results in nodular pulmonary amyloidosis and thus although it may be a helpful investigation it does not replace the need for a histological diagnosis [129, 130]. 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 [126, 127, 131]. Larger nodules can occasionally produce space occupying effects but otherwise no treatment is required.

Rarely pulmonary amyloid nodules have been reported to be transthyretin amyloid in type (ATTR). Wild type transthyretin amyloidosis is also known as senile systemic amyloidosis and usually presents with cardiac involvement although amyloidogenic transthyretin gene mutations are also well described [114]. Pulmonary involvement in senile systemic amyloidosis seems to be a rare incidental finding at autopsy [114]. A case report described by Roden et al., describes an 82 year old patient who presented with a diffuse nodular infiltrate and recurrent pleural effusions. Echocardiographic findings were consistent with cardiac amyloid. Biopsy of one of the lung tissue confirmed transthyretin amyloid by both immunohistochemistry and mass spectrometry. The TTR gene was found to be wild type by DNA sequencing [132]. Pulmonary nodules associated with AA amyloidosis have been found in patients with rheumatoid arthritis [133], Crohn's disease [134] and in patients with AA amyloidosis secondary to intravenous drug abuse [71] all have run a reportedly benign course.

Diffuse amyloid deposition within the lung parenchyma is usually associated with systemic AL amyloidosis (Fig. 7.6) with concomitant involvement of other organ systems [114]. Post-mortem series have confirmed that diffuse parenchymal amyloid is common in systemic AL amyloidosis although is symptomatic in a minority of cases [135, 136]. When pulmonary manifestations develop the disease is serious and

responds poorly to therapy. Patients are often very symptomatic frequently presenting with dysponea which may be further compounded by amyloid induced cardiac dysfunction. The pathophysiology is due to deposition of the 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 also 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.

As discussed above, clinical signs are often scant and sequelae are rare until late in the disease process. Radiographically the features can mimic a number of interstitial infiltrative diseases. Plain films often show a reticular pattern and on CT interstitial infiltrates are seen similar to more common interstitial lung diseases. Fine interlobular thickening is often seen peripherally and/or subpleuraly. The findings may be somewhat patchy depending on whether the fibrils are caused by local parenchymal populations of clonal plasma cells or from a distant 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. While this may rule out more metabolically active entities on the differential it is by no means a specific finding. As is the case with all forms of this disease, tissue is required to confirm the diagnosis and, as stressed throughout, is required to confirm the subtype in order to direct therapy. As AL amyloid is the most common aetiology and the process is most often diffuse and not amenable to surgical intervention the most appropriate treatment is chemotherapy aimed at the underlying plasma cell clone.

Pulmonary Amyloidosis Associated with Sjogrens Disease

Sjogrens disease is a chronic organ-specific autoimmune disease characterized by lymphocytic infiltration into the salivary and lacrimal glands which predominantly affects women [137]. It is associated with a 44 fold increase in lymphoproliferative disorders and can be divided into three stages according to the extent of organ damage and disease progression: stage I, accounting for 45 %, is sicca syndrome alone; stage 2, accounting for 50 %, includes lymphocytic damage to the pulmonary, renal, hepatic, haematological, and/or skin tissues. Approximately 5 % of patients develop stage 3 disease with 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. Sjogren's disease itself 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 [138]. Pulmonary amyloidosis is a rare but well recognised complication of Sjogrens disease and is most often associated with localised nodular pulmonary amyloidosis [139]. Amyloid deposits have also been noted to affect the breast tissues [140] and can result in a more systemic disease process [141]. A recent case series identified 33 cases in the literature 96.5 % of which were women with a median age at presentation of 59 years (range 29, 79) [142]. The most common symptoms were cough and dyspnoea. The majority of cases (91 %) occurred in primary Sjogren's disease and lymphoma was seen in 9 % of cases. The diagnosis of pulmonary amyloidosis was generally made some years after the initial symptoms of Sjogren's presented, with a median of 7 years (range 0, 30). Amyloidosis associated with Sjogren's is predominantly AL however there have been a few isolated case reports of diffuse septal AA amyloidosis without evidence of amyloid deposition elsewhere [143, 144].

Mediastinal and Hilar Amyloid Lymphadenopathy

Infiltration of 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 3 cases with associated mediastinal adenopathy [87]. Stage 3 Sjogrens syndrome complicated by secondary lymphoma is a recognised cause [87, 145]. The majority of patients with amyloid lymphadenopathy have a detectable circulating monoclonal immunoglobulin typically associated with very low grade lymphoplasmacytic lymphoma or Waldenstrom's macroglobulinaemia [146]. In this condition the hilar and mediastinal lymphadenopathy as well as results of the initial investigations can be highly suspicious for lung cancer and false positive PET findings have been described [147]. CT imaging of amyloid lymphadenopathy has demonstrated considerable variety; calcification is not uncommon and low density areas within lymph nodes have also been described [148]. The diagnosis is often made incidentally following a biopsy, and the discovery of amyloid should prompt the search for an underlying B-cell dyscrasia. Disease progression may be exceptionally slow and node calcification is well recognised [128, 149]. Amyloid adenopathy has occasionally been reported to cause tracheal compression and superior vena caval obstruction. Treatment centres on treating the underlying lymphoproliferative disease but surgical resection may become necessary.

Treatment

In the treatment of all amyloid based diseases the primary goal of therapy is to stop the production of amyloidogenic precursor. Short of surgical interventions, we have yet to come up with a widely available approach that leads to removal or degradation of amyloid deposits. We are thus limited to the body's own mechanisms for degrading these resilient and immunologically inert protein complexes. As one can imagine this happens in very few cases and tissue deposits often persist.

As described above the treatment approach to AA amyloid is to halt the underlying inflammatory process. If this occurs and there is longterm suppression of the circulating SAA protein a substantial amount of organ response is possible [55]. In the inherited forms of the disease only Apo AI is of any great significance in amyloid of the respiratory tract. Management is often guided by the presence of other organ involvement but in general short of liver transplantation, there is no available systemic therapy to halt the production of the precursor protein. Given the risks of the procedure transplanation is generally reserved for patients with significant multi-system involvement notably peripheral nerve and cardiac involvement, or of course those with progressive liver dysfunction.

The bulk of the disease burden in amyloidosis of the respiratory tract can be attributed to AL amyloid and as such we will focus on therapeutic strategies for this sub-type. The general principal of the therapy in any amyloid state revolves around the concept that local therapy is required for local disease and systemic therapy for more systemic disease. Local therapy ranges from surgical intervention to local radiotherapy while systemic treatment approaches generally involved chemotherapy directed at the underlying clonal B-cell based disorder.

In general amyloidosis involving the larger airways down to the bronchials is amenable to localized surgical measures. Localised laryngeal amyloid is usually relatively benign but can be progressive or recur after treatment. Fatal haemorrhage has been reported [150]. Following complete histological diagnosis and evaluation of the disease extent, endoscopic surgical [151, 152] or carbon-dioxide laser excision [153, 154] is the treatment of choice aiming to preserve voice quality and maintain airway patency [155]. 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 [156].

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 [115] the most common management strategy has been intermittent bronchoscopic resection or stenting [155], and carbon dioxide laser ablation or Nd:YAG laser therapy [157, 158]. Up to 50 % of patients respond poorly with only short term symptomatic relief [117]. Extensive airway involvement may require open resection [159]. Of the ten patients followed up by the Boston group, three died of respiratory complications, an average of 9 years after diagnosis, six patients underwent multiple laser resections and four required tracheostomies [115]. In contrast, three of four patients followed up by Cordier for a median of 8 years remained well [114]. Management therefore always needs to be tailored to each patient dependent on the degree of amyloid infiltration.

There is some evidence of successful results following external beam radiation therapy. While this approach does little to address the existing amyloid deposits it may help suppress the local plasma cell clone thus preventing progression. In laryngeal amyloid 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 [160]. External beam radiation therapy has also been reported in small series of patients with tracheobronchial amyloid [117, 161, 162]. Reports have suggested significant improvement in symptoms [117, 162]. Although long-term follow-up is limited the available data suggests that this strategy may well be the optimum management in patients with localised disease.

Involvement of the smaller airways and interstitium generally reflects a more diffuse pulmonary process and is often indicative of a more systemic disease process. In general it is not amenable to any surgical approaches. In addition the offending plasma cell population is often distant from the lung. As such, a systemic approach to treatment is usually required. There are, however, many difficulties that may be further compounded by the morbidiy associated with the pulmonary symptoms [163]. The majority of chemotherapeutic regimens are based on those used in multiple myeloma. Diagnosis is difficult and can be delayed with many patients having advanced multi-system disease limiting their options for chemotherapy [163]. Regression of amyloid is a gradual process which may not lead to measurable clinical improvement or recovery of organ function for many months, or even years, after successful suppression of the causative plasma cell dyscrasia [164, 165]. This is especially true of pulmonary involvement and other supportive agents such as inhaled medications are generally not helpful. The rate of mobilisation of amyloid deposits varies dependent on the organ. Cardiac amyloid deposits are much slower to show signs of regression compared to the liver or kidneys, and many patients with cardiac or multi-system dysfunction do not live long enough to

Table 7.5 Criteria for hematologic response

Response	Definition
Complete response	Serum and urine negative for a monoclonal protein by immunofixation
	Free light chain ratio normal
	Marrow <5 % plasma cells
Partial response	If serum M component >5 g/L, a 50 % reduction
	If light chain in the urine with a visible peak and >100 mg/day and 50 % reduction
	If free light chain >100 mg/L and 50 % reduction
Progression	From CR, any detectable monoclonal protein or abnormal free light chain ratio (light chain must double)
	From PR or stable response, 50 % increase in serum M protein to >5 g/L or 50 % increase in urine M protein to >200 mg/day; a visible peak must be present
	Free light chain increase of 50 % to >10 mg/dL (100 mg/L)
Very good partial response	Difference between involved light chain and uninvolved light chain is <40 mg/L
Stable	No CR, no PR, no progression[a]

Adapted from the 2005 criteria [169, 194]
[a]*CR* complete response, *PR* partial response

benefit from chemotherapy, even when it has succeeded in suppressing their clonal disease [166]. This trend appears to be shifting with the advent of more potent regimens incorporating novel agents. There is little information specifically examining pulmonary amyloid infiltrates however it is generally thought that they are fairly resilient and often evade significant degradation. However, despite these problems, many patients with AL amyloidosis do benefit substantially from chemotherapy [167] which has lead to improved clonal responses and survival outcomes in this disease [168].

Overall, the aim of treatment is to achieve adequate suppression of the pathologic light chain production with minimal toxicity. The clonal response is monitored routinely using the serum free light chain assay as well as serum and urine protein electrophoresis (Table 7.5). Organ responses have been defined for the more commonly affected organs but have not been formalized for pulmonary involvement [169]. In general, assuming parenchymal disease is present, the response is followed using pulmonary function testing at regular intervals and with change in symptoms. Reduction in serum free light chain levels is associated with improved overall and progression free survival [36, 170, 171]. The degree of response needed to halt production may be different for individual patients. Achieving a >90 % dFLC response (defined as the difference between the kappa and lambda serum free light chains before and after therapy) has been associated with improved patient outcome [171]. Importantly, it has also been associated with organ response with a higher chance of renal recovery [172]. A dFLC of <40 mg/L after therapy has also been suggested in recent guidelines as an optimal treatment endpoint [173].

Chemotherapeutic approaches are generally broken down into high-dose strategies incorporating stem cell transplantation and low-dose chemotherapy where the active agents are delivered over a longer period of time to minimize acute toxicity. The guiding principle in the treatment of this disease is that therapy needs to be tailored to the individual patient based on their organ involvement and functional status; balancing the beneficial effects of light chain suppression with the potential treatment associated morbidity and mortality. Prognostic staging systems have been developed to help guide the choice of treatment. The most widely used is the Mayo cardiac staging system based on cardiac dysfunction defined by the cardiac biomarkers tropoinin-T and NT-proBNP. Using cut off values of 0.035 mcg/L for Troponin T and 332 pg/mL for NT-proBNP, patients can be classified into three stages: Stage I, both biomarkers below cut off; Stage II one biomarker elevated and Stage III both biomarkers elevated. The reported median survivals are 26.4, 10.5 and 3.5 months respectively for Stages I, II and III [47].

High dose chemotherapy has been extensively investigated in AL amyloidosis. In general complete response rates are achieved in approximately 30 % of patients [174]. Overall survival is estimated to be between 5 and 8 years with two recent publications suggesting that this may exceed 10 year for those achieving a complete response. However, very rigorous patient selection for high dose chemotherapy is essential due to the high procedure related morbidity and mortality in individuals with multiple organ involvement [175]. In fact, less than 25 % of patients with AL amyloid will be eligible for this procedure. In an unselected patient population treatment related mortality may be as high as 20–30 % [176, 177]. It is generally accepted that cardiac stage III patients should be excluded from stem cell transplantation [178]. In addition, due to the poor respiratory reserve in patients with pulmonary parenchymal involvement, high-dose chemotherapy is often contraindicated as it contributes further to poor outcomes. Standard low dose chemotherapeutic options include the combination of melphalan and dexamethsaone as well as the triplet regimen of cyclophosphamide, thalidomide and dexamethasone [179–181]. Similar to stem cell transplantation complete responses are seen in approximately

30 % of patients although the responses tend to occur less rapidly. Overall survival is also similar at around 4–6 years although there is little published experience examining the durability of complete responses achieved using these strategies. Emerging experience with other novel agents including proteosome inhibitors [171, 182–184] and the second generation immunomodulory agents [185–187] are showing encouraging response rates and have had a marked impact on the management of these patients. Of particular interest is bortezomib which has been shown in a number of trials to be effective in the treatment of AL amyloidosis. Although the efficacy of proteosome inhibition is based on a number of different mechanisms, of particular relevance to AL amyloidosis is its role in "proteostasis" capitalizing on both the excess light chain production and accumulation of the mis-folded proteins [188, 189]. While the studies are small it appears that responses are both deep and rapid [171, 182–184]. Larger phase III trials with these drugs are currently under way to prospectively confirm the unprecedented complete response rates seen with these novel combinations. While numerous options exist for controlling the underlying fibril producing clone there is currently no strategy available that leads to disruption or degradation of the preformed fibrils. Recent advances in the laboratory using anti-SAP antibodies show some promise; an approach that might be more broadly applicable across amyloid sub-types [20]. Trials in human subjects are awaited.

Serious pulmonary side effects are extremely rare but have been described following the use of the proteasome inhibitor bortezomib. Patients present with fever and asthma like symptoms and progress to respiratory failure with pulmonary infiltrates on CT imaging [190]. There have also been case reports of lung toxicity following the use of thalidomide [191] and lenalidomide [192] 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 has also been associated with higher rates of thrombosis [193]. The recommendation is therefore to consider full dose anticoagulation in patients on thalidomide with nephrotic syndrome.

Conclusion

Amyloidosis is a heterogenous disease potentially impacting the respiratory system in a number of ways. In addition, respiratory conditions with a significant inflammatory component can themselves be the root cause of systemic amyloidosis; the treatment of which is required in order to suppress the fibril precursor protein and halt the disease. Respiratory conditions may also arise as a complication of systemic amyloidosis. Localised amyloid deposits can affect any level of the respiratory tract and may be asymptomatic, requiring no treatment or can lead complications which require intervention. This may range from localized surgical removal of the deposits to systemic therapy. Given the rarity of the condition the management of localised amyloid deposits are guided by small case series with treatment being tailored on an individual patient basis. While at present the bulk of the available therapeutic strategies focus on suppression of fibril production the development of drugs which interfere with fibrillogensis are on the horizon and may lead to a paradigm shift in the management of this disease in the future [20].

Clinical Vignette

A 58 years old woman who presented with a 12 month history of respiratory symptoms. She was a non-smoker and had no other significant past medical history. Initially, it was thought that the symptoms were due to angina. Cardiac investigations including angiography were unremarkable. Chest x-ray showed a reticular pattern chest x-ray and there was evidence of a restrictive defect on PFTs with impaired diffusion capacity. A subsequent CT showed evidence of interstitial lung disease prompting referral for biopsy. Review of the tissue showed evidence of diffuse interstitial amyloid deposition.

Key investigations were as follows:

- Hb 13.2 g/dL, WBC 14.6 × 10^9/L, Platelets 385 × 10^9/L
- Coagulation screen normal
- Creatinine 47 μmol/L, eGFR >90 ml/min
- 24 h urinary protein loss – 0.3 g, lambda Bence Jones Protein on immunofixation only
- Serum albumin 42 g/L
- Bilirubin 7 μmol/L, ALT 11 IU/L, AST 16 IU/L, ALP 81 IU/L, GGT 29 IU/L
- IgA <0.1 g/L, IgG 2.9 g/L, IgM 0.2 g/L with free lambda light chain paraprotein on immunofixation only
- Serum free light chains: kappa <0.3 mg/L, lambda 650 mg/L, K/L ratio >2,000
- NT-pro BNP 161 pMol/L, cardiac hs Troponin T 0.018 μg/L
- CRP 10 mg/L, SAA 9.4 mg/L
- ECG showed normal sinus rhythm with no features typical of amyloid involvement
- Echocardiogram showed a mean ventricular wall thickness of 10 mm, ventricular ejection fraction of 65 % with mild diastolic dysfunction. However, there were no classic features of cardiac amyloidosis. Elevated pulmonary arterial systolic pressure (35–40 mm/Hg) were present.

- SAP scintigraphy showed no significant abdominal visceral uptake.
- Biopsy of pulmonary parenchymal tissue showed diffuse interstitial amyloid deposits confirmed with Congo red staining. Immunohistochemical subtyping revealed that the amyloid was of lambda light chain origin.
- Bone marrow biopsy demonstrated a small population of lambda-restricted plasma cells (9 %).
- PFTs demonstrated a restrictive defect with diminished diffusion capacity
- CT demonstrated diffuse interstitial infiltration.

In summary, this is a patient with interstitial pulmonary amyloid confirmed to be of AL subtype on biopsy of the lung parenchyma. Subtyping by immunohistochemistry confirmed it to be of AL subtype (lambda light chain restricted). This is further supported by the small lambda restricted plasma cell clone in the bone marrow, monoclonal lambda light chain on serum and urine protein electrophoresis and lambda light chain excess on serum free light chain analysis. There is high risk of progression if left untreated. Despite her young age and the single organ system involvement high-dose chemotherapy and autologous stem cell transplantation was deferred due to her increased morbidity and mortality associated with the significant pulmonary deficits. A bortezomib based regimen was pursued (cyclophosphamide, bortezomib and dexamethasone). The cyclophosphamide was withheld after the first cycle due to the development of pneumonia requiring hospitalization. After 3 cycles of therapy she achieved a complete clonal response. Serial PFT's and follow-up of her symptoms will be used to assess her pulmonary organ-response. Given the resilience of amyloid fibrils this is not expected to occur for some time.

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8 Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome): A Clinical and Therapeutic Approach

Loïc Guillevin and Matthieu Groh

Introduction

Churg–Strauss syndrome (CSS) is a rare systemic small- and medium-sized–vessel vasculitis, which distinguishes itself from other small-vessel vasculitides by the presence of severe asthma, and blood and tissue eosinophilia. It was first described in 1951 by Jacob Churg and Lotte Strauss [1] and was initially called allergic angiitis and granulomatosis. In the forthcoming revision of the Chapel Hill Nomenclature, CSS will be renamed "eosinophilic granulomatosis with polyangiitis (EGPA)" (not yet published). Indeed, CSS patients' histological findings included necrotizing vasculitis, eosinophilic infiltrates and granulomas. CSS diagnosis is mainly based on clinical characteristics and can be confirmed by histology. Specific criteria, which are now reliable tools for classifying CSS among vasculitides [2], have been established. For now, CSS treatment still relies mainly on corticosteroids and, when necessary for patients with poorer prognoses [3], combined immunosuppressant drugs, especially cyclophosphamide. Overall survival of CSS patients is good, despite not uncommon relapses. New treatments or therapeutic modalities are being investigated to maintain durable remissions.

Pathophysiology

CSS etiology remains unknown. Its pathogenesis is thought to develop through three successive phases: asthma, blood and tissue eosinophilia, and, finally, vasculitis. However, not all patients experience this clear-cut stepwise progression of their disease, and symptoms of the different phases sometimes overlap. Because asthma is most common the first symptom of CSS, it has been hypothesized that the triggering pathogenic event might be an inflammatory response to inhaled antigens [4]. Furthermore, the discovery that patients with CSS flares often had higher levels of total serum IgE and IgE-containing immune complexes [5], initially supported the hypothesis that CSS might be an allergy-induced, immune-complex vasculitis. Initial clinical symptoms of seemingly atopic origin, like asthma, rhinosinusitis and nasal polyposis, seemed to support an allergic etiology. However, allergy concerns barely one-third of CSS patients [6]. Thus, different pathogenic mechanisms might account for the different CSS subpopulations.

A closer look at possible pathophysiological CSS subtypes found a clear clinical difference between patients with and without ANCA. Based on 2 distinct cohorts, described by Sinico et al. [7] and our group [8], ANCA frequency in CSS was ~40 %. Most often, CSS patients' ANCA have a perinuclear fluorescence-labeling pattern (P-ANCA), with anti-myeloperoxidase (MPO) specificity, as assessed by an enzyme-linked immunosorbent assay (ELISA). In both studies, CSS patients with anti-MPO ANCA suffered more, albeit not exclusively, from vasculitis symptoms, such as glomerulonephritis, mononeuritis multiplex and alveolar hemorrhage, than ANCA-negative patients [7, 8].

The pathogenic role of anti-MPO ANCA has been demonstrated in vitro and in vivo. First, anti-MPO ANCA are able to activate neutrophils, leading to the production of reactive oxygen species and the release of lysosomal proteolytic enzymes contained in neutrophil granules, causing subsequent vascular damage [9]. Second, these antibodies might also affect the vascular endothelium itself, as they can increase vessel-wall permeability, thereby inducing vascular endothelial cell expression of numerous cytokines, such as interleukin (IL)-1, IL-6 and IL-8, and intercellular and vascular cell-adhesion molecules. Finally, through experimental passive transfer of anti-MPO ANCA into mice, their roles in

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developing vasculitis and, most consistently, glomerular nephritis, were confirmed in vivo [10, 11]. Hence, although these antibodies might explain the predominance of vasculitis manifestations, like glomerular nephritis, in patients who express them, they might not be implicated in others.

Notably, for ANCA-negative patients, other factors are obviously needed to induce vasculitis. Among them, eosinophils might play predominant roles. Indeed, eosinophils are constantly present at diagnosis, and appear to be activated during flares, as suggested by their surface expression of CD25 and CD69 [12]. In addition, CSS patients' sera, bronchoalveolar lavage fluids, bronchial biopsies and urine specimens contain elevated levels of eosinophil cytotoxic proteins, including eosinophil cationic protein, eosinophil major basic protein, eosinophil-derived neurotoxin and eosinophil peroxidase [13], which are known to be directly implicated in tissue damage.

Eosinophil activation in CSS requires specific cytokine stimulation. This role is partly ensured by CSS patients' T cells, which predominantly exhibit an activated TH2 phenotype, resulting in the secretion of high levels of IL-4, IL-13 and IL-5 [14]. Those 3 cytokines, especially IL-5, are essential for eosinophil activation, maturation and survival. Moreover, the reported close relationship between disease activity and IL-5 concentrations [15] suggested prominent roles of eosinophils and, for that matter, IL-5–secreting T lymphocytes in CSS pathogenesis. More recent studies even showed the possible cross-talk between eosinophils and TH2-type lymphocytes in CSS, via the secretion of IL-25, a potent TH2-response enhancer, by the eosinophils themselves [15]. This and other factors, e.g. high levels of soluble CD95 impairing eosinophil-apoptosis [16], might account for the persistent eosinophilia in active CSS. Eotaxin-3, a chemokine strongly secreted by endothelial and inflammatory cells in CSS patients' damaged tissues, seems to attract eosinophils towards affected tissues [17].

Other cells are also apparently implicated in CSS pathogenesis, especially TH1-type lymphocytes, that secrete cytokines, such as interferon-γ and soluble IL-2 receptor [18], possible inducers of granuloma formation. Thus, the coexistence of TH1- and TH2-type cytokines in CSS led to the hypothesis that variations of the TH1- and TH2-helper T-cell balance at different disease stages could be partially responsible for the different clinical courses, ranging from TH1-mediated granulomatous vasculitis to TH2-mediated systemic hypereosinophilia [19]. However, that explanation might very well be too simplistic and outdated. Other protagonists of CSS pathogenesis seem to include regulatory T cells (Treg) [20], and TH17 and Tr1 cells [21]. Finally, the results of several studies highlighted the potential contributions of certain predisposing genetic factors, e.g., *HLA-DRB1*04* and *DRB1*07* alleles, the *HLA-DRB4* gene and the *IL-10.2* haplotype [22, 23]. Hence, although advances have been made in our understanding of CSS pathophysiology, the existence of different pathogenic patterns accounting for the histological, clinical and biological heterogeneity of CSS patients is possible.

Epidemiology

Incidence and Prevalence

CSS is a rare disease and its prevalence, in the general population, ranges from 10.7 to 13 [24] cases/million inhabitants, with an annual incidence of 0.5–6.8 new cases/million inhabitants [25], depending on their geographical location and the classification criteria applied. Among the asthmatic population, the CSS incidence is higher, ranging from 34.6 [26] to 64.4 [25] cases/million patient-years. Notably, the CSS incidence among asthmatics remains approximately the same, independently of their prior treatment, especially concerning their use of leukotriene-receptor antagonists. CSS can occur all ages, with a mean age at diagnosis of 48 years [27], and shows no clear sex predominance.

Triggering Factors

As discussed previously, CSS seems to develop after an inflammatory response to antigens. This pathophysiological conclusion was based the numerous patients described as having developed CSS after being exposed to certain triggering factors. Among the latter, certain infectious agents (*Actinomyces* [4] for example), drugs, such as macrolides, carbamazepine and quinine, and, finally, allergic hyposensitizations and vaccinations [4] have been reported.

We recently vaccinated a population of patients with vasculitis, including some with CSS, against H1N1 (non-adjuvant vaccine). Most patients tolerated the vaccine well, with only a few of them showing increase numbers of blood eosinophils [28]. No patient relapsed. The benefit/risk ratio favors vaccination, even though we have to consider that some anecdotal patients could flare after vaccination. Notably, we still do not recommend hyposensitization for patients with active disease and eosinophilia.

Other triggers have been considered, particularly the use of anti-asthmatic drugs, like the leukotriene-receptor antagonists, montelukast and zafirlukast [29–31], and, more recently, the recombinant anti-IgE monoclonal antibody, omalizumab [32]. However, it is increasingly accepted that the corticosteroid-tapering allowed by these drugs, and not the drugs themselves, might favor CSS flares, thereby unveiling "forme frustes" of the disease not previously diagnosed in severely asthmatic patients [29–31, 33]. The authors of a recent case–crossover study [29] concluded that the

Table 8.1 Main clinical manifestations of Churg–Strauss syndrome

Parameter	Chumbley et al. (1977) [35]	Lanham et al. (1984) [36]	Gaskin et al. (1991) [37][a]	Comarmond et al. (2012) [39]	Abu-Shakra et al. (1994) [38]	Guillevin et al. (1999) [27]
Number of patients	30	16	21	383	12	96
Male/female sex ratio	21/9	12/4	14/7	199/184	6/6	45/51
Mean age (years)	47	38	46.5	50.3	48	48.2
Manifestation						
Asthma	100	100	100	91	100	100
General symptoms	–	–	–	–	100	70
Lung infiltrates	27	72	43	38.6	58	38
Pleurisy	–	29	–	8.9	–	–
Ear, nose and throat	70	70	–	41.8	83	47
Mononeuritis multiplex	63	66	70	46	92	78
Gastrointestinal	17	59	58	23	8	33
Cardiac	16	47	15	27.4	42	30
Arthralgias	20	51	43	29.8	42	41
Myalgias	–	68	–	38.9	33	54
Skin	66	–	50	39.7	67	51
Purpura	–	48	–	22.5	–	31
Nodules	27	30	–	8.9	–	19
Kidney involvement	20	49	80	21.7	8	16

Results are expressed as percentages unless stated otherwise
[a]Nephrology department patients

montelukast–CSS link could be drug-related, essentially as a consequence of steroid-tapering, or be purely coincidental, with the drug having been prescribed to treat already present CSS that had not yet been diagnosed.

Clinical Features

In addition to the respiratory tract, which is almost constantly involved in CSS as asthma, any organ system can be affected, either through eosinophil infiltration, granuloma or, most frequently, vasculitis. Once the vasculitic process begins, systemic symptoms appear, often accompanied by organ-associated vasculitic symptoms, like mononeuritis multiplex and necrotic vascular purpura. Once CSS is suspected, vasculitis involvements of the gut, kidney and/or heart must be sought, because of their proven significant association with poorer prognoses [34]. Below, we describe the main clinical symptoms of CSS. Notably, their frequencies varied widely among studies [27, 35–39], as summarized in Table 8.1.

Initial Symptoms

CSS is most commonly revealed by the onset of vasculitis manifestations – mononeuritis multiplex, purpura and general symptoms – and eosinophilia, in a previously asthmatic patient. However, some patients may develop asthma or eosinophilia simultaneously with vasculitis and, albeit very rarely, in the weeks following its onset [27]. The clinical presentation of these ANCA-positive patients differs significantly from that of ANCA-negative patients, with more frequent mononeuritis multiplex and glomerular nephritis in the former, and more cardiomyopathy in the latter [7, 8]. Based on differences in the clinical symptoms observed in patients with and without ANCA, we suggested [8] that CSS might be divided into different clinical and pathophysiological subtypes, which could be managed better with more specifically adapted therapies.

General Symptoms

General symptoms, primarily fatigue, malaise, fever (58 %) and weight loss, are usually the first and foremost manifestations of this vasculitis. In a previously asthmatic patient, these symptoms, in conjunction with eosinophilia, should alert the clinician to a possible CSS flare.

Pulmonary Manifestations

Lung involvement, as noted above, is almost universal in CSS patients. Asthma (96–100 % of patients) [8, 27] most often precedes systemic vasculitis (mean interval: 8.9 ± 10.9 years) [27], but sometimes occurs simultaneously or later. The mean age of asthma onset in the future CSS patient is about 30 years. It is often severe, corticosteroid-dependent and associated with ear, nose and throat symptoms, including rhinitis (70 %), nasal

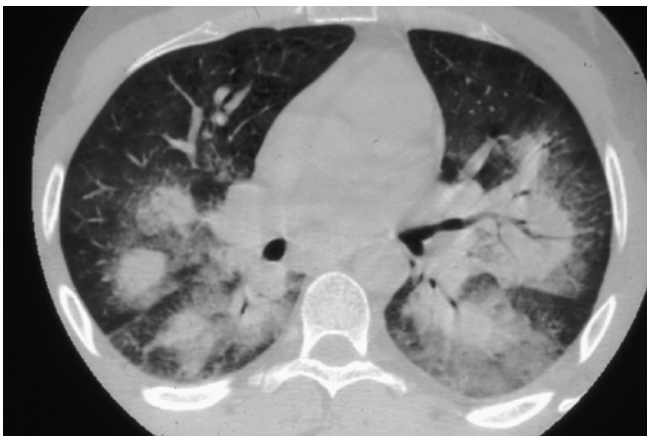

Fig. 8.1 Thoracic computed-tomography scan showing bilateral lung haemorrhages

obstruction, nasal polyposis and sinusitis (62.5 %) [27]; the latter is never destructive as in Wegener's granulomatosis. Evidence shows that both rhinitis and asthma in CSS are less often allergy-related than among non-CSS asthmatic patients [6]. Typical lung radiographic findings are patchy and transient alveolar infiltrates. Alveolar hemorrhage, due to pulmonary small-vessel vasculitis is another, much less common, CSS manifestation (Fig. 8.1). It occurs predominantly among anti-MPO ANCA-positive patients [7, 8]. Dyspnea due to phrenic palsy has sometimes been described. Finally, pleural manifestations exist but are rare. CSS pleural effusions are often asymptomatic and are mainly characterized by eosinophil-rich exudates. Pleural vasculitis is rarely observed, representing only 2/96 (2.1 %) of our previously reported patients [27]. Mediastinal adenopathy is sometimes seen, usually when cardiomyopathy is present.

Neurological Manifestations

Peripheral neuropathies are the second most common extrapulmonary manifestations of CSS, mainly mononeuritis multiplex, due to peripheral nerve vasculitis of the vasa nervorum. The most frequently involved nerves are the common peroneal (66 % of patients) [27], ulnar, internal popliteal and, to a lesser degree, radial and median nerves. Signs and symptoms are those of mononeuritis: motor palsy, sensory deficiency (hypo- and sometimes painful hyperesthesia) and muscular atrophy. Recovery is long and unpredictable. Cranial nerve palsies are much rarer (1 %). Polyneuropathy and Guillain–Barré-like syndromes have been described [40].

Central nervous system involvement is much less frequent. Clinical manifestations vary widely, ranging from hemiplegia to seizures, and rare subarachnoid hemorrhages. Computed-tomography (CT) scan efficiently diagnoses ischemic or hemorrhagic complications, but cannot attribute those manifestations to cerebral vasculitis. Magnetic resonance imaging (MRI) can detect T2-weighted signals in the subcortical white matter, which are highly evocative of vasculitis.

Skin Manifestations

Cutaneous involvement is diverse and frequent (40–70 %) in CSS patients. Two different mechanisms account for that diversity of skin lesions: vasculitis and extravascular granuloma. Vascular purpura was described in about half of published cases and 31.2 % of our patients [27], and predominantly affects the lower limbs. Other vasculitic manifestations include livedo reticularis (6.2 %), urticaria-like lesions (8.3 %) [27], Raynaud's syndrome, vesicles and infiltrated papules. Subcutaneous nodules containing extravascular granulomas are present in about one-third of CSS patients. Clinically, they are red or violaceous, sometimes painful, nodules, preferentially located on the extensor surfaces of the elbow, fingers and scalp.

Gastrointestinal Involvement

Digestive tract involvement of CSS carries a poor prognosis [34, 41]. All types of histological lesions may be found: extravascular granulomas, which sometimes mimic polypoid lesions; tissue eosinophilia, presenting as eosinophilic enteritis and potentially affecting the entire gastrointestinal tract; and, finally, vasculitis, which is responsible for ulcerative ischemic lesions. The latter are the most severe, because they can be the origin of potentially fatal complications of intestinal hemorrhage and bowel perforation. Abdominal pain is a common CSS symptom, present in 30–60 % of the patients, along with nausea, vomiting and diarrhea. Sometimes, no intestinal lesions are found and abdominal pain may recede with treatment.

Heart Manifestations

Cardiac involvement is also responsible for a dismal prognosis, as it is the major cause of morbidity in CSS patients and the first cause of their mortality (48 % of deaths) [27]. Its frequency varies among studies, ranging from 15 to 84.6 %. Notably, 35 % of Sablé-Fourtassou et al. 112 CSS patients had cardiac manifestations [8]: 25 % with pericarditis and 24 % with myocarditis. Cardiac involvement was much more frequent in ANCA-negative than -positive patients (49 % vs. 12 %, respectively) [8], and 22.4 % vs. 5.7 %, according to Sinico et al. [7], suggesting that heart manifestations might mostly be due to mechanisms other than coronary vasculitis,

e.g., myocardial granulomas or eosinophil toxicity. These manifestations include eosinophilic myocarditis, but also coronary vasculitis, heart valvulopathy [42], congestive heart failure, hypertension and pericarditis.

Complementary cardiac investigations are mandatory to evaluate clinically symptomatic patients and useful to detect cardiac involvement in asymptomatic patients, as non-negligible numbers of them have anomalies. These investigations comprise chest X-ray, electrocardiogram, echocardiography, and N-terminal pro-brain natriuretic peptide and troponin I dosages. Cardiac MRI (CMRI) is crucial to confirming CSS cardiac involvement, revealing inflammatory pericardial involvement, microvasculitis of the epicardial and myocardial vessels, and inflammation and/or fibrosis of the endocardial or myocardial tissue [43, 44]. One of our recent prospective studies showed that, while CMRI usually confirmed all cases of suspected (symptomatic) heart involvement (9/9 cases), it could also detect cardiac anomalies (visualized as delayed gadolinium enhancement of the myocardium) in almost 40 % of asymptomatic patients (4/11 patients) but the meaning of those findings remains uncertain [44, 45]. Comparing positron-emission tomography (PET) to CMRI showed that the former could detect active disease, whereas the latter is not always able to differentiate among activity, healing processes and sequelae [46].

Rheumatological Manifestations

These symptoms include arthralgias, usually without arthritis, and myalgias: 53 % of our patients had polyarthralgias, predominantly affecting the large joints, whose evolution often paralleled that of the vasculitis, but no joint deformation was observed. Myalgias are present in 53.6–68.7 % [8, 27] of CSS patients, especially during the acute phase of vasculitis.

Renal Manifestations

Kidney involvement is usually rare, compared to other ANCA-associated vasculitides. Only 16 % of our patients had renal involvement, consisting of merely mild proteinuria, hematuria and/or arterial hypertension [27]. However, because rapid crescentic glomerulonephritis (Fig. 8.2) causes higher mortality, making an early diagnosis is crucial. Serum creatinine levels exceeding 140 µmol/l (150 in the revisited version of the five-factor score (FFS) [34]) is another poor-prognosis factor [34]. Glomerular nephritis in CSS is usually associated with anti-MPO ANCA-positivity [7, 8]. However, other histological findings may be encountered: renal vasculitis, eosinophil-rich interstitial infiltrates and granulomas.

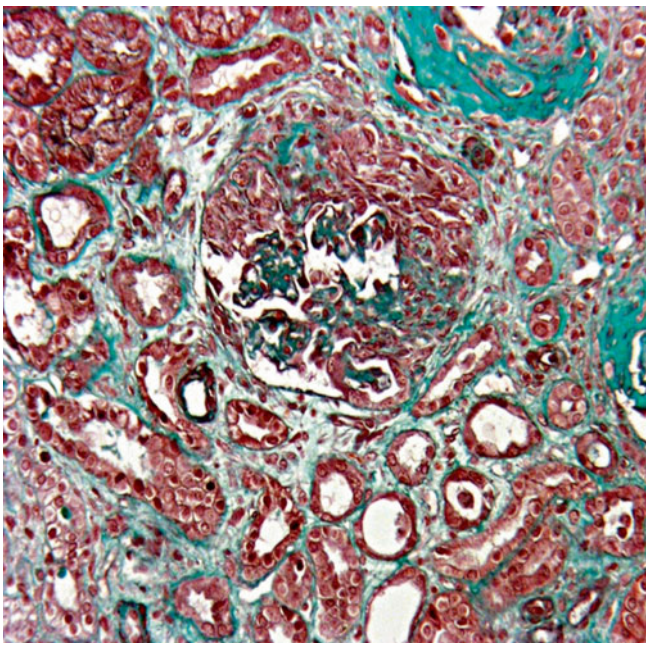

Fig. 8.2 Renal biopsy showing segmental necrotizing glomerulonephritis with crescents and interstitial inflammatory cell infiltrate. Masson's trichrome stain, ×200

Miscellaneous

Eye involvement is rare in CSS. Ocular manifestations include: episcleritis, conjunctival nodules (consisting of extravascular granulomas), keratitis, posterior uveitis [47], ocular palsies and ischemic optic neuropathies.

Other particular organ locations have been described, for example, ureteral granulomas and stenosis, widespread digestive involvement [48, 49] or temporal arteritis mimicking giant-cell arteritis [50].

Finally, some apparently limited forms of CSS have been described [51, 52]. They concern patients with asthma, hypereosinophilia and single-organ involvement without systemic symptoms. Most often, the gut is involved as eosinophilic enteritis. In forms initially limited to the lung, the differential diagnosis with chronic eosinophilic pneumonia may be particularly difficult [53]. These two entities sometimes overlap, as cases of CSS preceded by chronic eosinophilic pneumonia have been described [54]. The existence of limited forms of CSS remains controversial, especially when clinical symptoms are associated only with eosinophilia, and their diagnosis is probably overestimated.

Complementary Investigations

Blood hypereosinophilia, high IgE titers and anti-MPO P-ANCA–positivity are the 3 main laboratory anomalies found in CSS. Inflammation is present in 80 % of these

patients; it is intense and often accompanied by anemia (83 %) [27].

Eosinophilia fluctuates during CSS but is a constant symptom. An eosinophil count exceeding 1,500/mm^3 or 10 % of the total white blood cell count has been retained as one of the diagnostic criteria for CSS [36]. We compared the accuracy of the absolute number of eosinophils vs the percentage to diagnose CSS and found them comparable [55], with mean values of the former ranging from 4,400 to 8,190 [7, 8, 27]. But eosinophils may disappear rapidly once corticosteroids are started. Eosinophilia is a relatively reliable marker of CSS activity, as an eosinophil rise may precede relapse. However, during follow-up of our patients, we frequently observed isolated eosinophil increases, usually between 1,000 and 1,500/mm^3, although sometimes more, which remain difficult to interpret in the absence of clinical symptoms. Usually, this phenomenon occurs during steroid tapering; in that case, eosinophil values normalize when the steroid dose is again raised, sometimes by as little as 1 or 2 mg/day. Such isolated eosinophilia warrants careful monitoring but should not be considered sufficient to diagnose a CSS relapse. It is probably a predictive marker of relapse or a limited form of relapse, since recrudescence of asthma and eosinophilia preceded relapses with systemic manifestations in half of our patients (Guillevin, unpublished observations).

IgE is elevated at diagnosis in 75 % of patients but is nonspecific, and is usually not seen in patients taking corticosteroids for their asthma. That observation further questions the role of allergy in CSS pathophysiology and explains why omalizumab, an anti-IgE monoclonal antibody, may sometimes be used to treat CSS.

ANCA, predominantly P-ANCA of anti-MPO specificity, are present in ~40 % of CSS patients but some can be directed against proteinase 3 (PR3). ANCA titers do not correlate with disease-evolution characteristics, although the authors of 1 study [56] favored a link between high ANCA titer and relapse. Unfortunately, that study included mainly microscopic polyangiitis and Wegener's granulomatosis patients; furthermore, recruitment was based solely on laboratory immunological findings, which might have skewed interpretation of data.

Rheumatoid factor-positivity was reported for 22 (53.7 %) of the 41 published cases [36, 57]. Antinuclear antibodies are usually absent.

Bronchoalveolar lavage fluid can contain eosinophils [58]. Renal involvement should be sought by measuring the serum creatinine level and urinalysis, to search for proteinuria and hematuria. Finally, biopsies with histological evidence of granulomas (18 %), tissue eosinophilia (52 %) and/or necrotizing small-vessel vasculitis (55 %) also contribute to diagnosing CSS [8].

Among imaging techniques, chest X-ray should be the first examination. In our experience, it revealed abnormalities in 37.5 % of the patients [27], who had bilateral and migratory infiltrates or mixed interstitial patchy alveolar opacities, which can be further evaluated by thoracic CT scans.

Abdominal angiography, when performed, may show typical stenoses consistent with vasculitis in up to one-third of the patients [27], extremely rarely associated with microaneurysms. It may be informative for suspected mesenteric vasculitis, when other diagnostic methods fail. Angiography (conventional, CT scan or MRI) is not recommended before renal biopsy because CSS renal manifestations (glomerulonephritis) are usually associated with ANCA and involvement of larger vessels has not been described.

The systematic detection of cardiac abnormalities is important because of their poor prognosis. Coronary arteriography may be decisive in detecting underlying ischemic cardiopathy, distinct from CSS cardiomyopathy. Recently, CMRI was shown to be better at detecting myocardial involvement in CSS patients [44–46]. After gadolinium injection, T1-weighted cardiac sequences may reveal centromyocardial, subepicardial and/or subendocardial myocardial delayed enhancement. While CMRI always confirms symptomatic myocardiopathy, it may also help identify asymptomatic cardiac abnormalities that go undetected by other techniques. However, whether these patients will indeed develop patent cardiomyopathy and, thus, be at greater risk of death, has not yet been elucidated., Notably, unlike CMRI, cardiac PET scans are able to visualize the activity of lesions [46].

Diagnosis

Today, CSS diagnosis is essentially based on clinical manifestations and histology. The onset of vasculitis symptoms, such as mononeuritis multiplex or purpura in conjunction with systemic symptoms of fatigue, weight loss and fever, in a previously asthmatic patient are highly suggestive of CSS. Eosinophilia and anti-MPO ANCA further corroborate the diagnosis. Finally, although not mandatory, histological proof of CSS can confirm the diagnosis, with skin, nerve and muscle biopsy sites having the highest respective sensitivities of 67.4, 65.7, and 47.9 % [27]. For example, biopsies confirmed CSS for 91.6 % of our patients [27].

Histological Findings

Initially, CSS diagnosis of was mainly based on histological findings, characterized by the 3 known defining pathological lesions: small- to medium-sized–vessel vasculitis; eosinophil infiltration of the arterial wall and adjacent tissues; and, finally, extravascular granuloma. During CSS, virtually any

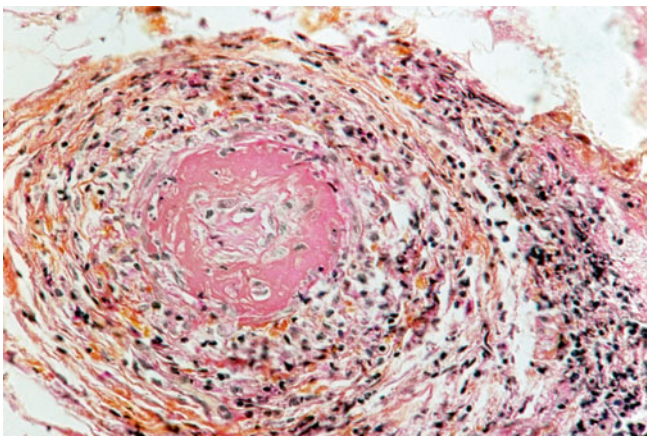

Fig. 8.3 Deep skin biopsy showing intraluminal thrombus, fibrinoïd necrosis and intense interstitial inflammatory cell infiltrate containing eosinophils. Hematoxylin, eosin and saffron stain, ×400

organ can be affected. During the acute phase of this vasculitis, arterial wall inflammation is characterized by fibrinoid necrosis of the media, and pleomorphic cellular infiltrates, predominantly eosinophils, around and inside the arterial wall. This lesion slowly progresses towards complete vessel fibrosis, resulting in the obliteration of its lumen (Fig. 8.3). Extravascular granulomas, although quite characteristic of CSS, are neither constant in nor specific to CSS [59, 60], as they can be seen in other vasculitides, such as Wegener's granulomatosis, or autoimmune diseases. Finding all 3 lesions on a single biopsy is very rare, and less than a fifth of the patients' specimens will satisfy all 3 pathological criteria simultaneously [61]. This observation has led to decreased reliance on histological features alone, as they are considered too stringent for diagnosing CSS.

Diagnostic Criteria

A clinical redefinition of CSS, established in 1984 by Lanham et al. [36], has allowed clinicians diagnose CSS with good specificity and sensitivity without relying on histological findings. The 3 diagnostic criteria are asthma, blood eosinophilia exceeding 1,500/mm^3, and evidence of vasculitis involving 2 or more organs. However, that definition has been criticized: first, asthma may follow and not precede the vasculitic phase; second, eosinophilia may sometimes fluctuate and disappear, either spontaneously or after starting corticosteroids; and, finally, vasculitis, despite certain characteristic clinical manifestations, may be hard to confirm without a biopsy.

Other criteria have been proposed, especially for classification purposes, notably the American College of Rheumatology [62] and Chapel Hill criteria [2]. However, those criteria are not diagnostic, as their goal is to classify patients as having a probable diagnosis of CSS, but only once vasculitis is already the presumptive diagnosis. New diagnostic criteria currently being discussed include, for example, anti-MPO ANCA, and clinical and biological redefinitions of CSS.

Box 8.1
Eosinophilic Granulomatosis with Polyangiitis: Diagnostic Criteria

At present, no validated diagnostic criteria for Churg Strauss syndrome (CSS) exist. In 1956, Churg and Strauss described pathological features of their eponymic syndrome. In 1984, Lanham et al were the first to propose clinicopathological criteria. To date, both in clinical practice and scientific publications, the American College of Rheumatology and Chapell Hill classification criteria are the most commonly used. In the absence of documented evidence of vasculitis, these classification criteria may be unable to differentiate between CSS and other hypereosinophilic syndromes.

Lanham (or Hammersmith Hospital) 1984 Criteria

1. asthma
2. peak peripheral blood eosinophil count >1,500/mm^3
3. systemic vasculitis involving ≥2 extrapulmonary organs

When all three criteria are met: diagnostic sensitivity and specificity are both 95 %.

American College of Rheumatology 1990 Criteria

1. asthma
2. eosinophilia >10 % of the differential white blood cell count
3. mono- or polyneuropathy attributable to systemic vasculitis
4. non-fixed pulmonary infiltrates
5. paranasal sinus abnormality (history of acute or chronic paranasal sinus pain or tenderness, or radiographic opacification of the paranasal sinuses)
6. extravascular eosinophils on biopsy

When at least four of these six criteria are met, diagnostic sensitivity and specificity are 85 and 99.7 %, respectively.

The Chapel Hill 1994 Consensus Conference Definition of CSS

1. asthma
2. eosinophilia
3. eosinophil-rich and granulomatous inflammation involving the respiratory tract
4. necrotizing vasculitis affecting small- to medium-sized vessels

Differential Diagnosis

The differential diagnosis of CSS depends on each patient's predominant clinical manifestations. Before vasculitis onset, concomitant eosinophilia, asthma and lung infiltrates may resemble certain parasitic infections, like helminthiases, or allergic bronchopulmonary aspergillosis. At this stage, it may be difficult to differentiate chronic eosinophilic pneumonia from CSS [53]. However, when systemic vasculitis manifestations appear, asthma and a somewhat lower sensitivity to corticosteroids tend to favor a diagnosis of CSS.

Hypereosinophilic syndrome (HES) is another differential diagnosis difficult to distinguish, because some HES patients may have neuropathy, albeit rarely mononeuritis multiplex, and cardiopathy and pulmonary manifestations [63]. The main differences tilting the pendulum in favor of CSS are: ANCA, vasculitis manifestations or biopsy-confirmed vasculitis and, finally, a somewhat lower eosinophil count. However, for most patients suspected of having CSS, especially those without ANCA or biopsy-proven vasculitis, lymphocyte immunophenotyping, clonal T-cell studies and molecular analyses to detect Fip1-like 1 (*FIP1L1*)–platelet-derived growth factor receptor-alpha (*PDGFA*) gene fusion, to search for lymphoid or myeloid HES forms, should probably be performed.

Once vasculitis becomes predominant in the clinical picture, the main differential diagnoses of CSS are other systemic vasculitides, especially Wegener's granulomatosis and polyarteritis nodosa. Whereas CSS and polyarteritis nodosa share numerous clinical characteristics, like mononeuritis multiplex, articular and muscular lesions, and gastrointestinal symptoms, CSS is usually easily distinguishable by asthma, atopic history, eosinophilia and lung infiltrates [1]. Kidney lesions in CSS are glomerular and, thus, different. Finally, Wegener's granulomatosis, another ANCA-associated vasculitis that shares common characteristics with CSS is usually ruled out by the presence of asthma, eosinophilia, non-destructive sinus involvement, mononeuritis multiplex and, when present, the anti-MPO–specific ANCA (versus anti-PR3 in Wegener's granulomatosis) [64, 65].

Prognosis and Outcome

CSS prognosis is generally good, even though historically, before the advent of corticosteroid therapy, it was almost always fatal. CSS prognosis has been revolutionized by the use of corticosteroids and immunosuppressant(s). Whereas in 1950, the 5-year survival of patients with polyarteritis nodosa (not yet separated from CSS) was 10 %, today, the overall 5-year survival of CSS may reach 88.7 % [39]. However, not all CSS patients share the same prognosis, as it depends on the initial degree of disease extension and number of organs involved. The original, prognostic FFS [66] was obtained by univariate and multivariate analyses of 342 vasculitis patients, including 82 with CSS. The 5 factors (each accorded 1 point) conferring a higher risk of mortality rate were: (1) proteinuria >1 g/24 h; (2) serum creatinine level >140 (150 μmol/l in the revised FFS [34]); (3) myocardial involvement; (4) severe gastrointestinal involvement; and (5) central nervous system involvement. Adding the assigned points gives clinicians a strong prognostic indicator of mortality, since patients with FFS = 0, 1 or 2 had increasing 5-year mortality rates of 12, 26 or 46 %, respectively. The FFS helps identify which patients who, because of their higher risks of relapse and mortality, require more aggressive immunosuppressive treatment.

The revised the FFS was based on a new analysis of 1,108 consecutive patients suffering from systemic necrotizing vasculitides, including Wegener granulomatosis [34]. The following five criteria, each again accorded 1 point, are now significantly and independently associated with higher 5-year mortality: (1) age over 65 years; (2) cardiac symptoms; (3) gastrointestinal involvement; (4) renal insufficiency characterized by serum creatinine >150 μmol/l; and (5) the absence of ear, nose and throat manifestations. According to this new definition, revised FFS = 0, 1 or 2 is associated with respective 5-year mortality rates of 9, 21 or 40 %.

The vasculitis itself is the main cause of CSS patients' deaths, accounting for almost half (47.6 %) of them [27]. Cardiomyopathy (39 %) is the first cause of CSS-related mortality, attributed to refractory cardiac insufficiency or sudden death, while the second is gastrointestinal complications, especially mesenteric infarction (8.7 %). Pertinently, first-year mortality largely resulted from uncontrolled vasculitis (66 %) [67] in patients with cardiac, renal and/or severe gastrointestinal involvement. Other causes of death mainly include respiratory disease (17.4 %), e.g., end-stage respiratory failure and severe status asthmaticus, and iatrogenic complications (17.4 %) [27]. Although two-thirds of patients develop at least 1 treatment-associated side effect, most of them are reversible, non-severe and not responsible for CSS mortality. However, authors of more recent therapeutic studies have incriminated infection-related deaths as most assuredly being linked to potent immunosuppressive therapy [3].

Another major concern of CSS is relapse. Although approximately 90 % of patients enter remission [27], including those with poor-prognosis factors (87.5 % who received pulse IV cyclophosphamide), the overall relapse rate was 25.6 % [27], and reached 73.8 % for other poor-prognosis patients not given maintenance therapy [3] and 35 % for good-prognosis patients treated with corticosteroids alone [68]. Although the mean interval between remission and relapse was 69.3 months [27], most relapses occurred during the first year of follow-up [3, 68] and, apart from an

eosinophilia rise [27], seem difficult to predict. These observations stress the importance of maintenance, corticosteroid-sparing therapies and eosinophil monitoring.

Treatment

The choice of therapy for patients with newly diagnosed CSS depends on their prognosis at diagnosis determined with the original FFS. For all patients, the objective is to induce clinical remission as quickly as possible, and then to sustain it as permanently as possible. Although CSS has a low overall mortality rate, approximately one-quarter of all patients relapse within 5 years after diagnosis. The relapse rate after 5 years of follow-up has not been studied extensively. Some patients relapse with systemic manifestations and others present only recrudescence of asthma and eosinophilia. It is unclear whether such manifestations should be considered a relapse or if they are only signs of eosinophilic asthma.

Steroid therapy remains the hallmark of CSS treatment. As induction therapy, prednisone is prescribed to good- and poor-prognosis patients at a dose of 1 mg/kg/day. Methylprednisolone pulses (15 mg/kg) may also be used for 1–3 days to obtain rapid control of life-threatening general symptoms. The duration of induction therapy depends on the clinical symptoms, with 3–4 weeks usually being necessary. After this period, steroids are tapered to reach 5–10 mg/day by the 12th month.

For patients without poor-prognosis factors (original FFS = 0), corticosteroids alone, as induction and maintenance therapy, have been evaluated. In the CHUSPAN study [68], the 5-year survival rate for this population was excellent (96.6 %), further validating the FFS. However, only 55.6 % of patients achieved complete remission, and one-third (34.6 %) of the patients eventually required a cytotoxic drug, 16.6 % because steroids alone failed and 25 % because of relapse. In that study on good-prognosis patients [68], 93 % entered remission with steroids alone, but 35 % relapsed, often during the first year of follow-up, and 79 % of them required persistent low-dose corticosteroids. For 26 % of those patients, eventual adjunction of a cytotoxic drug was necessary to control their disease. Hence, while a certain number of CSS patients respond adequately to steroids alone, another subgroup with good initial prognosis might also require more potent immunosuppressants. At present, it is not possible, based on clinical or biological criteria, to determine which are the patients require immunosuppressant adjunction to control good-prognosis forms of the disease, spare corticosteroids or prevent relapse.

Different cytotoxic agents have been given to good-prognosis patients in an attempt to limit relapses [69]. For this indication, cyclophosphamide is not useful for most patients and has a low benefit/risk ratio [70]. IV methotrexate (0.3 mg/kg/week), despite allowing significant corticosteroid-sparing in 56 % of patients, failed to lower the relapse rate [71]. Finally, azathioprine is currently being evaluated (CHUSPAN 2) as a steroid-sparing agent in CSS without poor-prognosis factors. Often however, even after obtaining vasculitis remission, some patients still need maintenance with corticosteroids, if only to control their asthma. Indeed, 88.1 % of our patients still required low-dose oral prednisone (8.9 ± 6.8 mg/day) during long-term follow-up [27]. In addition, because most patients receive long-term steroids, other treatments, such as vitamin D, calcium and bisphosphonates, should also be prescribed to avoid corticosteroid-related complications.

For patients with at least 1 poor-prognosis factor (original FFS ≥ 1), cytotoxic drugs are always necessary to induce remission. Induction therapy with pulse cyclophosphamide (0.6–0.7 g/m^2) is the most common choice because of its high efficacy and more limited side effects, compared to oral administration. Notably, pulse cyclophosphamide combined with corticosteroids achieved complete remissions in 87.5 % of 48 such patients [3]. However, in that study without maintenance therapy, relapse rates were high, ranging from 73.8 to 85.7 %, depending on whether patients had received 6 or 12 cyclophosphamide pulses, respectively, and corticosteroid use was prolonged, as 81.2 % of the patients were still taking low doses for asthma and relapse prevention after 8 years of follow-up. Nevertheless, overall survival was still very good, reaching 97 and 92 %, respectively, at 5 and 8 years.

Hence, once poor-prognosis patients obtain remission, maintenance therapy with a less toxic immunosuppressant is essential, as is done for Wegener's granulomatosis. Azathioprine remains the drug of choice. Although the optimal duration of maintenance therapy is still unknown, it is widely accepted that this regimen should last at least 18–24 months [72].

Despite induction and maintenance therapies, relapses and mild asthma or vasculitis-symptom persistence underscore the need for new therapies. Rituximab has been used sporadically and successfully for ANCA-positive patients [73], and is currently being evaluated at the Mayo Clinic in an open-label study on patients with renal involvement (ClinicalTrials.gov, NCT00424749). Despite the efficacy observed in some of our patients, rituximab should be prescribed very prudently, as two of our patients experienced severe bronchospasms immediately after its first infusion, despite concomitant administration with IV steroids [74].

Because of its antagonist effect on TH2-mediated immune responses, interferon-alpha was prospectively evaluated in an open-label study [75]. Although it apparently achieved acceptable remission rates, its effect was transient and relapses occurred often after ending treatment. Another

factor limiting its widespread use is its potential cardiac toxicity. This drug seems to have a limited place in the treatment of CSS.

Omalizumab, a murine anti-IgE antibody, may be effective in some patients, but has been incriminated as a possible CSS-triggering factor [32, 76] and, thus, should not be recommended. Mepolizumab, an anti-IL-5 antibody, showed promising results. In a small series of patients, the drug was able to control the disease while reducing the steroid dose [77]. Other agents have been used occasionally, for example IV immunoglobulins as an alternative to cytotoxic drugs during pregnancy [78, 79], or as rescue therapy for patients with refractory neuropathy or cardiomyopathy [80]. By analogy with other ANCA-associated vasculitides [81], plasma exchange may be useful for ANCA-positive CSS patients, especially those with rapid crescentic glomerulonephritis and pulmo-renal syndrome.

Finally, good CSS management also includes other important therapeutic adjuncts. Adequate treatment of asthma must be pursued, as it often evolves independently of the vasculitis. *Pneumocystis jiroveci* prophylaxis with co–trimoxazole (400 mg/day or 800 mg thrice weekly) should be prescribed to patients receiving cyclophosphamide. Finally, physiotherapy has an integral part in treating peripheral neuropathy motor deficiencies and sequelae.

Clinical Vignette

A 52-year-old man, with a 3-year history of asthma, was diagnosed with Churg Strauss syndrome (CSS) in July 2007: late asthma, non-fixed pulmonary infiltrates, sinusitis, eosinophilia (13.9 cells/mm^3), myocarditis, arthralgias and myalgias. Anti-neutrophil cytoplasm antibody (ANCA) serology was negative. Because of his heart involvement, six cyclophosphamide pulses were added to conventional steroid therapy.

Two months after diagnosis, the patient was admitted to the intensive care unit in cardiac arrest. The electrocardiogram showed asystole, attributed to severe hyperkalemia, and renal failure caused by decompensated steroid-induced diabetes and treatment with angiotensin-converting–enzyme inhibitor. Cardiopulmonary resuscitation and adrenaline restored normal electrical activity. His condition improved with insulin and volume resuscitation. Azathioprine was started as maintenance therapy, but caused toxidermia and was rapidly switched to mycophenolate mofetil.

In January 2008, when beta-blockers were started, the patient's condition worsened. Cardiac magnetic resonance imaging revealed severe dilated cardiomyopathy, mitral regurgitation, subepicardial delayed contrast enhancement in the septum (Fig. 8.4) and anterior wall, and T2-weighted hyperintensity in the same myocardial territory (Fig. 8.5), consistent with edema. These findings indicated active CSS-related cardiomyopathy. He underwent heart transplantation

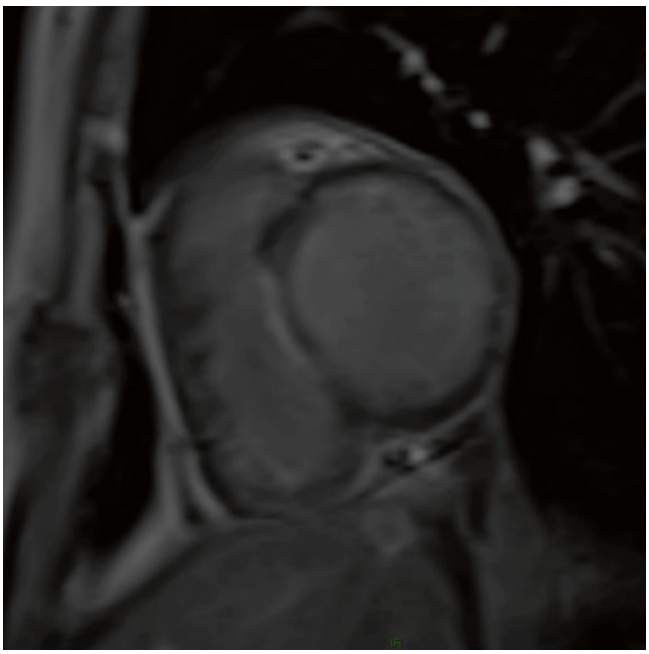

Fig. 8.4 Short-axis view. Three-dimensional delayed-enhancement T1-weighted gradient-echo inversion-recovery magnetic resonance image (repetition time: 1.4 ms; echo time: 600 ms; inversion time: 250 ms) shows septal myocardial delayed enhancement

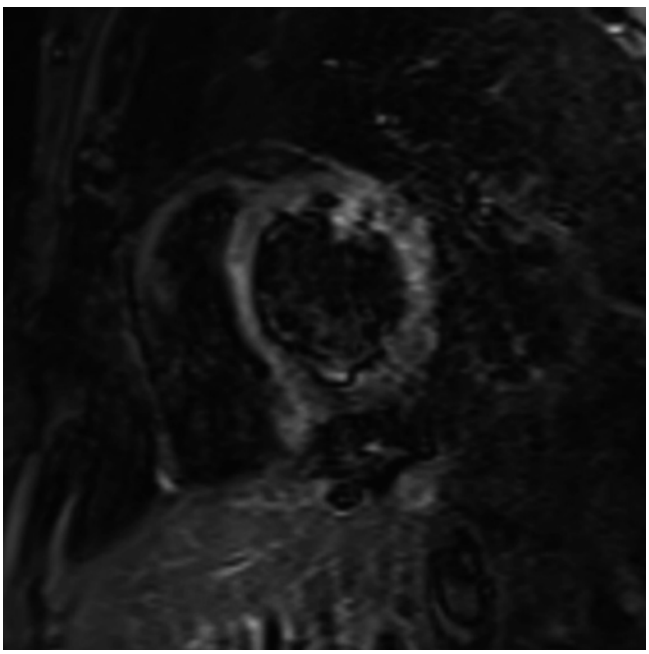

Fig. 8.5 Short-axis view. Two-dimensional inversion recovery, black blood fast spin-echo image (repetition time: 700 ms; echo time: 47 ms; inversion time: 170 ms) shows septal myocardial T2-weighted hyperintensity consistent with oedema

on 13 March 2008. Despite numerous post-operative complications (septic mediastinitis, septic shock associated with *Enterobacter aerogenes* ventilator-associated pneumonia, acute *Cytomegalovirus* infection, ICU peripheral polyneuropathy and chronic diarrhea caused by *Enterocytozoon bieneusi*), the patient achieved full neurological and functional recovery. However, he developed chronic kidney disease (serum creatinine 205 μmol/L).

Four years after heart transplantation on a regimen combining prednisone, cyclosporine and mycophenolate mofetil, no major CSS relapse or graft rejection, based on regular endomyocardial biopsies, has occurred.

Conclusion

Much progress has been made over the past 30 years in understanding, redefining and treating CSS. Management of CSS patients is now more effective and, thus, its good prognosis is even better, compared to other vasculitides. However, what is becoming ever more apparent is the broad heterogeneity of CSS patients' phenotypes. New patient subsets have been identified, with the most obvious being those with and without ANCA, as their clinical presentations differ. Moreover, these clinical variations might represent pathophysiological differences. Therefore, more research is needed to understand fully the mechanisms underlying different CSS manifestations and, hence, to devise specific treatment regimens, when possible.

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Granulomatosis with Polyangiitis (Wegener's Granulomatosis)

9

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Granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis, is a systemic vasculitis characterized by necrotizing granulomatous inflammation predominantly affecting small-sized vessels [1, 2]. It is rare, but the incidence has increased within the past decades, at least in some northern countries, in part, but possibly not exclusively, because of better recognition [3]. GPA primarily affects adults between 45 and 60 years old but can affect people of all ages. Upper and lower respiratory tracts and/or kidney manifestations are the cardinal signs of the disease; several are quite suggestive, such as saddle-nose deformity or lung nodular cavitations. Constitutional symptoms such as fever, fatigue and weight loss are common [4]. GPA is typically associated with anti-neutrophil cytoplasm antibodies (ANCA) with a diffuse cytoplasmic labelling pattern (cANCA) seen on indirect immunofluorescence and directed towards proteinase 3 (PR3) on ELISA. The etiology remains unknown, although knowledge of the major pathophysiological mechanisms, however complex, has greatly improved in recent years [5, 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 corticosteroids, others (namely, rituximab) have recently been found effective and possibly less toxic, at least for the late risks of infertility and, perhaps, late cancers. However, the rate of relapse remains high, which results in the need for prolonged maintenance immunosuppressive therapy, with unknown optimal duration, and continual search for newer therapies [7]. In addition, a few patients experience refractory disease, unrelenting relapses despite treatment and/or particularly challenging manifestations such as subglottic stenosis or retroorbital pseudotumor, for which treatment can be much more difficult.

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Brief Historical Overview

The clinical picture of nasal cartilage destruction consistent with the diagnosis of GPA but also with that of nasal natural-killer-cell lymphoma (previously known as lethal midline granuloma) was described in 1897 by McBride, an English otorhinolaryngologist. The subsequent published cases of GPA with histologic 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, Fahey, Churg, 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 [8], then the Chapel Hill consensus [2], which confirmed in 1994 the position of the disease within the necrotizing, systemic small-sized vessel vasculitides (Table 9.1). In 2011, Wegener's granulomatosis was officially renamed granulomatosis with polyangiitis after delayed gathering of evidence that Friedrich Wegener had some involvement in the Nazi Party during World War II and in a broader effort to eliminate medical eponyms [9]. International efforts since the 2011 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 [10].

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Table 9.1 Classification criteria and definition of granulomatosis with polyangiitis (Wegener's granulomatosis), according to the American College of Rheumatology (1990) [8], the nomenclature of the consensus conference held in Chapel Hill (NC) in 1993 [2] and revised in 2012 [10]

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)
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*
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*
Microscopic polyangiitis*
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
** These vasculitides are associated with ANCA*
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

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 9.2), but young children and older adults can be affected. Most patients (93–98 %) are white (Caucasian and Hispanics). The estimated annual incidence is 2–12 cases per million population and the prevalence 23–160 cases per million population [3]. A north-south gradient is suggested, at least in Europe, because the reported annual incidence is twice as high in Norway, for example, than in

Table 9.2 Characteristics of patients with granulomatosis with polyangiitis (Wegener) and frequency (percent), according to the main studies published between 1958 and 2011

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

Spain (10.6 vs. 4.9 per million inhabitants) [11]. Conversely, antiPR3+ GPA is rare in Japan, where anti-myeloperoxidase (antiMPO) + disease (mostly microscopic polyangiitis-type) represents most cases of ANCA vasculitis. Notably, the incidence of the disease seems also to have increased within the past decades, according to several European studies, although whether these changes could be related, at least in part, to a better understanding of the disease and thus lead to more frequent and earlier diagnosis, especially since the discovery of ANCA in 1985, remains controversial [12]. A recent British study suggested peaks of incidence every 8–10 years (17.4 per year per million population during peaks vs. only 4.53 per year per million population not during peaks) [11]. Seasonal variations in GPA incidence have been reported, but with conflicting results.

The existence of these potential geographic and temporal variations in GPA incidence suggest a potential pathogenic, or at least participating, role of environment (allergic, chemical and/or infectious) and/or genetic factors in the development of the disease. The association of 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 [13]. 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 [14]. Finally, an inverse relation between the intensity of sun exposure, specifically ultraviolet rays, and GPA prevalence suggests a possible link with vitamin D deficiency, as has been suggested in many other autoimmune diseases [15].

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) [16]. Personal (and probably also familial) history of autoimmune thyroiditis has been found more frequently in GPA than in the general population (13 % of GPA patients) [17]. Factors related to genetic predisposition are thus likely, although not enough to explain or trigger the disease by themselves. Several international teams are conducting studies on genome-wide associations with GPA. Many variable genetic associations have indeed been reported, the two most reproducible being those for molecules of major histocompatibility complex (MHC) *HLA-DPB1*0401* (odds ratio [OR] 3.38 for patients with ANCA) 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) [18]. 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 -alpha receptors, intracellular tyrosine phosphatase *PTPN22* (620 W allele), transforming growth factor-beta 1, interleukin-10 (IL-10) promoter, CTLA-4, or CD226 (Gly307Ser) polymorphism allele [18, 19]. GPA has been associated with other MHC molecules, including DR2 and DR4 allele 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 healthy subjects.

More importantly perhaps, results of recent studies showed that genetic susceptibility was more linked with the ANCA type (antiPR3 with *HLA-DP* and the genes encoding α1-antitrypsin (*SERPINA1*) and proteinase 3 (*PRTN3*); antiMPO with *HLA-DQ*) than with the clinical phenotype (GPA versus microscopic polyangiitis) [20]. Whether the classification of ANCA-associated vasculitides should be modified according to these results is now under debate.

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 ANCA in 1985 [12]. However, the primum movens of the disease remain(s) to be identified [5, 6].

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 shown in one study, possibly by maintaining a local inflammatory immune response within the nasal mucosa [21]. A selective cross-reactivity of T cells towards 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 protein-complementary idiotype–anti-idiotype mechanism [22]. 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 [23]. Other organisms could also be involved. Recently, anti-lysosomal membrane protein 2 (antiLAMP2), another and newer type of ANCA, was detected by Kain and colleagues in more than 90 % of patients with ANCA-related (antiPR3 as well as antiMPO) glomerulonephritis [24]. This group further showed the LAMP-2 epitope with 100 % homology to the bacterial adhesin FimH located at the tip of type 1 fimbriae and crucial for attachment to host epithelia of Gram-negative pathogens such as *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus mirabilis*. In addition, pauci-immune glomerulonephritis developed in rats immunized with FimH. However, those results have not been replicated and thus remain controvertial [25].

Whatever the signal for their synthesis, PR3-ANCA are detected in more than 80 % of patients with generalized GPA. However, their pathogenic role is less well documented than that of pANCA antiMPO (most characteristic of microscopic polyangiitis). Until recently, convincing animal models of vasculitis associated with antiPR3 ANCA were lacking as compared with those associated with antiMPO. In the mouse model of Pfister et al., vasculitis induced by transfer of antiPR3 ANCA remained localized to the mouse footpads, was not granulomatous and required prior sensitization with subcutaneous injections of tumor necrosis factor a (TNF-α) [26]. In the BALB/c murine model of Pendergraft et al., mice did not develop overt vasculitis [22]. More recently, two murine models of antiPR3 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) [27, 28]. Specific alterations and "maturation" may be necessary for antiPR3 ANCA to become pathogenic, including the selection of higher-affinity ANCA in the nasal mucosa granulomas or modulation of their sialylation levels [29]. Although the pathogenicity of anti-PR3 ANCA remains difficult to demonstrate, results from recent studies of therapies targeting B cells (i.e., rituximab) provide indirect evidence for their potential role, unless these biologic agents act through other more complex pathways [30–32].

Other factors or mechanisms involved in GPA can favor or enhance the PR3-antiPR3 ANCA immune response or act independently. Besides the frequent functional and/or genetic deficit in α-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 (cellular activation debris produced in response to inflammatory signals), were found to express PR3 and MPO, thus perpetuating the presentation of self-antigens, and could trigger or increase inflammatory responses in endothelia, especially in kidneys [33, 34]. GPA has been associated with excess production of certain soluble factors of stimulation and proliferation of B lymphocytes (B-cell activating factor 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 co-stimulatory molecules, including increased membrane expression of CTLA4, can lead to rupture of immune tolerance mechanisms.

The binding of ANCA results in activation of the alternative complement pathway and production of reactive oxygen species by neutrophils, all of which lead to endothelial injury (depletion of neutrophils or blockade of complement pathway both prevent the development of antiMPO-induced vasculitis in experimental models) [35, 36]. Granuloma formation, an important histologic characteristic of GPA, involves lymphocyte subpopulations, with a preferential cytokine secretion profile of TH1 lymphocytes (interferon-gamma), but also other complex cytokine imbalances, cell populations or immune pathways of more recent discovery, such as TH17 lymphocytes, a source of IL-17, dendritic or natural killer cells. 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 the GPA and their frequencies are in Table 9.2. 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. Complications of treatment and disease damage 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 Manifestations

More than two-thirds of the patients have ear, nose and throat manifestations, which often represent the first symptoms of the disease. When isolated, such symptoms can result in diagnostic delay. Persistent nasal obstruction, nasal or sinus pain, sinusitis, rhinitis, recurrent epistaxes and/or nasal crusting, or serous otitis media and/or hypoacousia should alert physicians to the possibility of GPA [4]. 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. 9.1), is very suggestive although not pathognomonic of GPA [37, 38]. The cartilage of the ears can also be affected (chondritis), as can osteochondral tissues of the face and skull, with rare occurrence of palate perforation or development of fistulas between sinus and orbital cavities.

Another classic but rarer upper-respiratory-tract lesion (7–15 % of patients) is subglottic stenosis, which is responsible for dysphonia, dyspnea, with or without stridor, and may require emergency procedures (dilatation with local injections of corticosteroids or tracheostomy) [38, 39]. Subglottic stenosis can be associated with endobronchial stenoses or can be isolated. It can parallel other manifestations or continuously progress despite control of disease elsewhere [40].

CT scan of the sinuses may show unilateral or bilateral sinusitis, osteochondral destruction and/or osteosclerosis (Fig. 9.2), otitis media and/or mastoiditis. Granulomatous inflammatory pseudotumors can also occur and can infiltrate the sinuses, skull base and/or orbits and be responsible for pain, proptosis, or contiguous pachymeningitis, which incur risk of compression of surrounding structures, such as cranial (ophthalmoplegia) or optic nerves. CT scan findings of Subglottic stenosis should be studied in parallel with 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

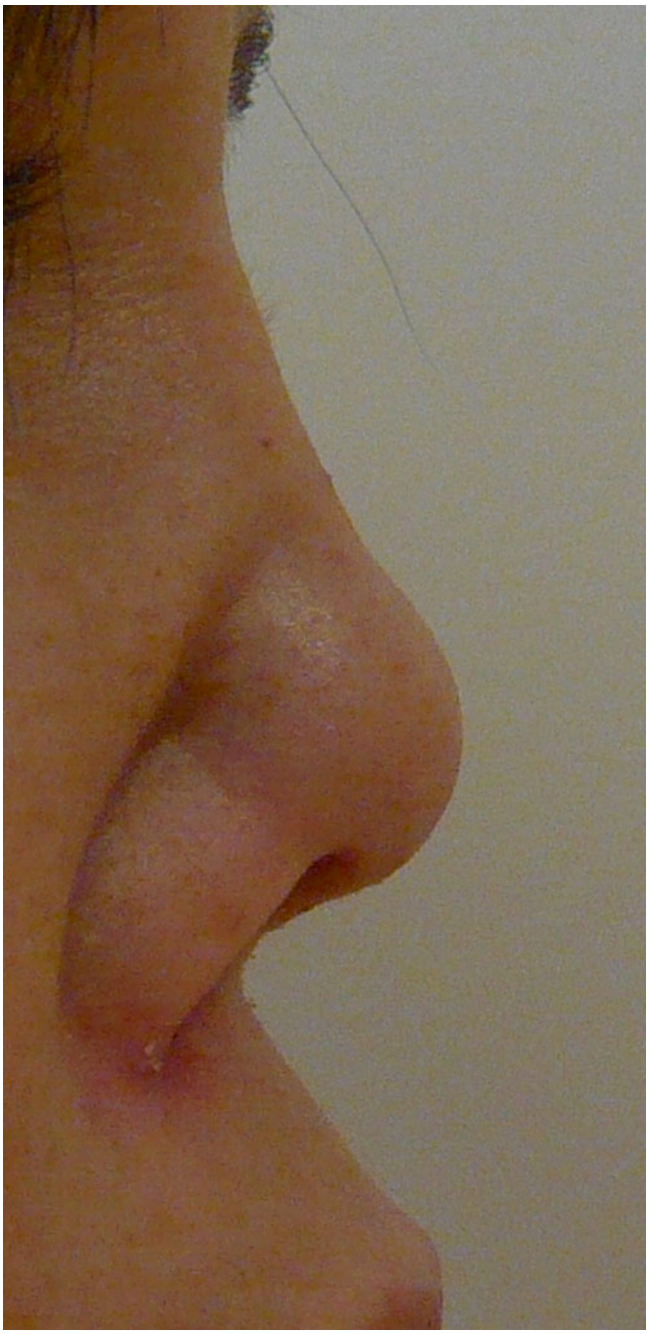

Fig. 9.1 Nasal deformity (bridge erosion) in a patient with granulomatosis with polyangiitis (Wegener)

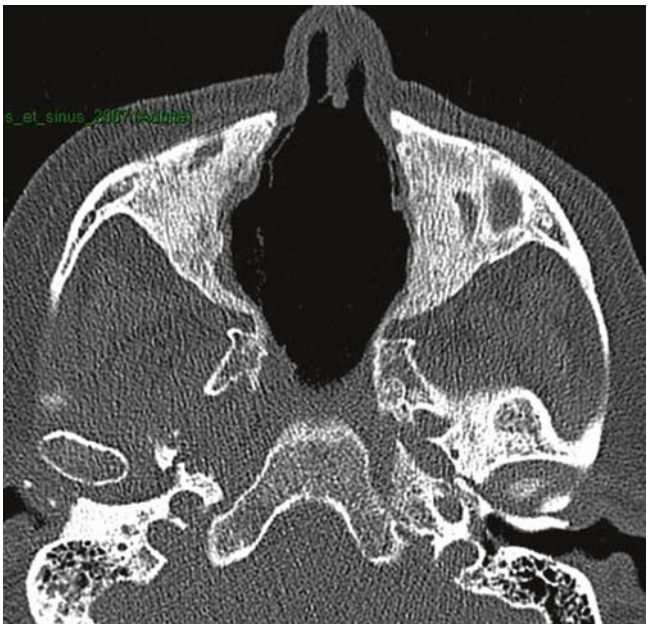

Fig. 9.2 Sinus CT scan (horizontal) in a patient with granulomatosis with polyangiitis (Wegener). Major destruction of septum and midline cartilaginous structures, along with bilateral maxillary sinus osteosclerosis and atrophy

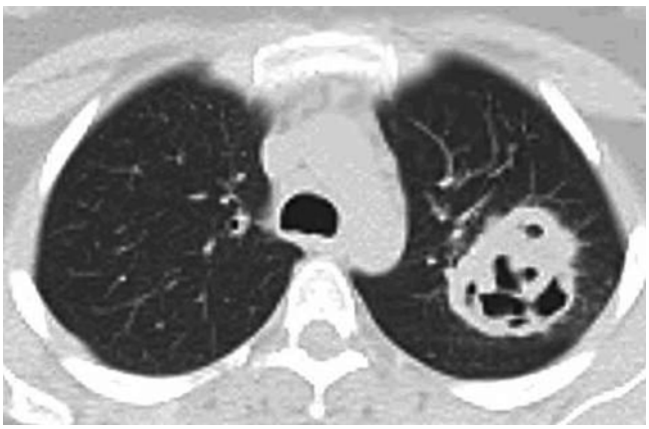

Fig. 9.3 Chest CT scan (horizontal) in a patient with granulomatosis with polyangiitis (Wegener). Large parenchymal excavated nodule (left lung)

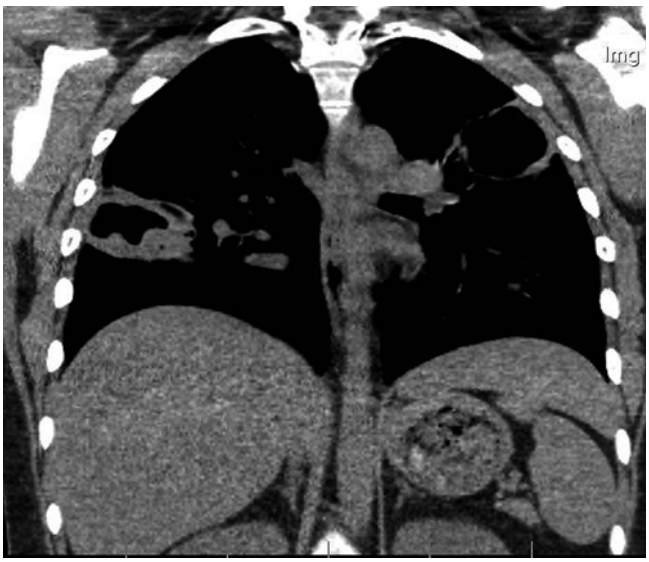

Fig. 9.4 Chest CT scan (coronal) in a patient with granulomatosis with polyangiitis (Wegener). Large parenchymal excavated nodules in both lungs

the mucosa [41, 42]. In routine practice, nasal and sinus biopsies are often superficial and rarely contribute to diagnosis (abnormal in <25 % of cases).

Pulmonary Manifestations

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. Chest X-ray and CT scan can show nodules in 40–66 % of patients [43]; nodules are unilateral or bilateral, single or multiple (generally <10), measuring 0.5–10 cm in diameter, and excavated in half of cases (Figs. 9.3, 9.4, 9.5, and 9.6). 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 in chest X-ray. The differential diagnosis, including primary or metastatic tumors and tuberculosis or fungal infections, can be difficult.

Alveolar hemorrhage (8–30 % of patients) can occur at symptom onset or later and be associated with lung nodules [4]. 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 chest CT scan (Figs. 9.6, 9.7, and 9.8; patchy, ground-glass opacities) and/or as unexplained anemia, then confirmed by broncho-alveolar lavage (demonstrating persistently hemorrhagic fluid on sequential samples). Even when overt, broncho-alveolar lavage should be considered to rule out concurrent infection, even at disease onset.

Other pulmonary infiltrates or lung consolidation (Fig. 9.5), unilateral or bilateral, may be observed in 30–50 % of patients and pleural effusion in 9–28 % [4, 43]. Spontaneous pneumothorax or pyopneumothorax is rare but can occur. Bronchial stenoses, usually on main bronchia and/or first branches, are uncommon and are often difficult to

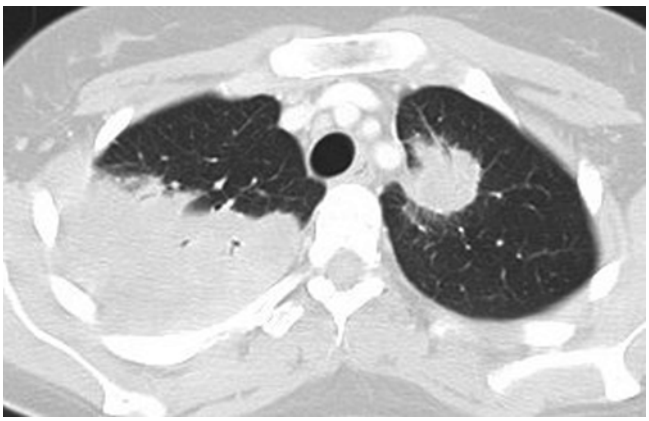

Fig. 9.5 Chest CT scan (horizontal) in a patient with granulomatosis with polyangiitis (Wegener). Parenchymal plain nodule (left lung) associated with right lung posterior consolidation (and mild pleural effusion)

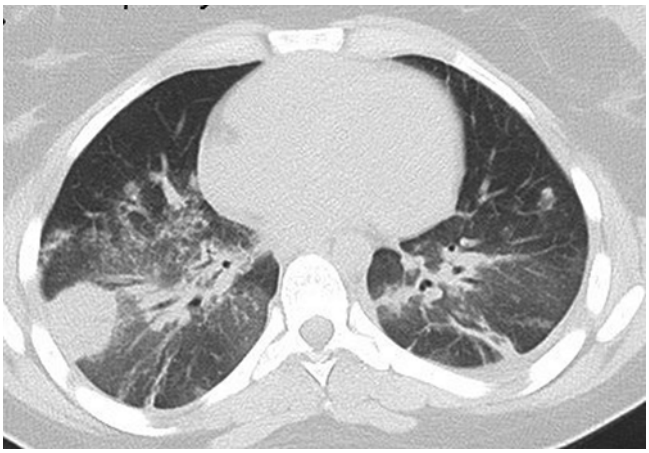

Fig. 9.6 Chest CT scan (horizontal) in a patient with granulomatosis with polyangiitis (Wegener). Parenchymal plain nodule (right lung) associated with multiple bilateral patchy opacities and diffuse posterior ground glass opacities (probably corresponding to moderate alveolar hemorrhage)

manage, as mentioned previously (frequently associated with subglottic stenosis). These are best studied with CT scan of lungs (Fig. 9.9) and fiberoptic bronchoscopy, which can reveal multifocal strictures and/or granulomatous endobronchial lesions.

Surgical and open-wedged lung biopsies, targeting nodules or consolidation lesions, have good diagnostic yield, up to 91 % [4, 42]. 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) should be considered a sign of active GPA, especially in patients with otherwise unexplained chest pain and/or sudden shortness of breath.

Asthma is not a feature of GPA and may suggest eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome).

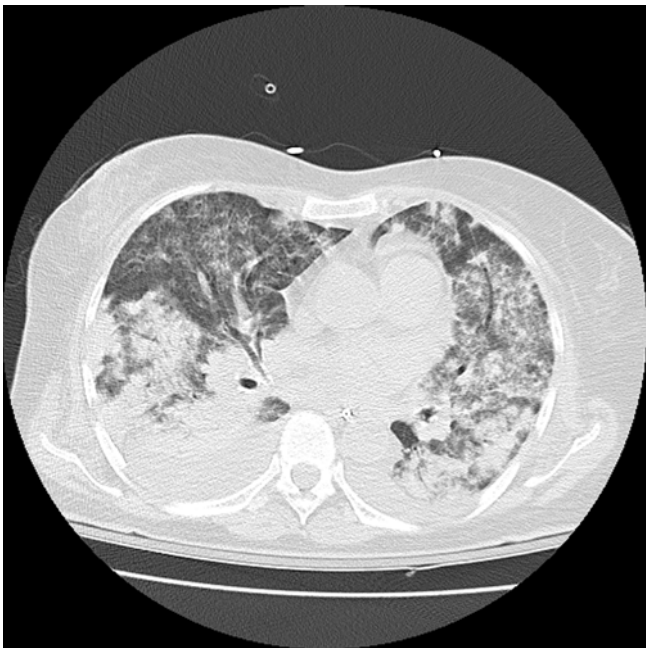

Fig. 9.7 Chest CT scan (horizontal) in a patient with granulomatosis with polyangiitis (Wegener). Diffuse bilateral ground glass infiltrate corresponding to massive alveolar hemorrhage

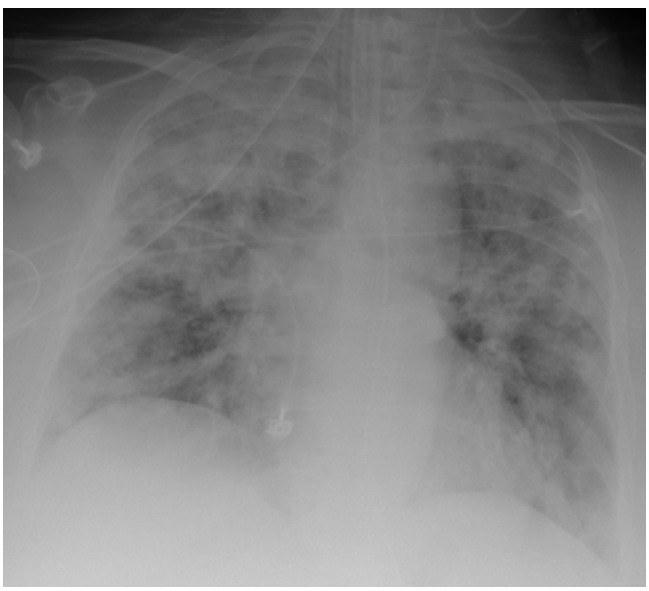

Fig. 9.8 Chest radiograph (anteroposterior) in a patient with granulomatosis with polyangiitis (Wegener). Diffuse bilateral bronchoalveolar infiltrate corresponding to massive alveolar hemorrhage

Coincidental association of the two conditions remains possible, and an eosinophilic variant form of GPA has been described, sometimes with asthma. Chronic interstitial lung disease with fibrosis is not a classical feature of GPA, as compared to antiMPO-associated lung fibrosis with or without systemic vasculitis (microscopic polyangiitis), but has been reported.

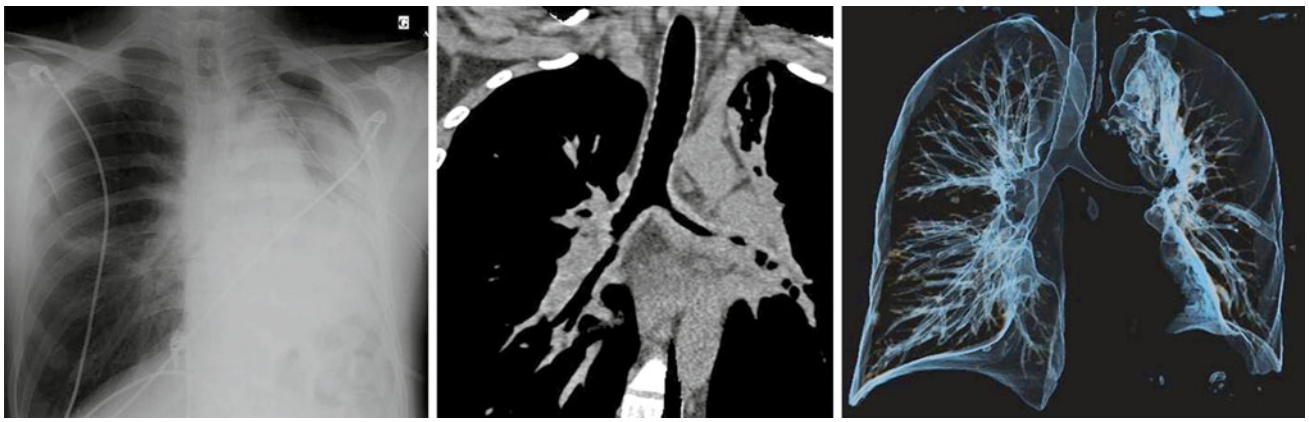

Fig. 9.9 Chest radiograph (anteroposterior), CT scan (coronal) and 3D-volume reconstruction of the tracheobronchial tree in a patient with granulomatosis with polyangiitis (Wegener). Major lengthy and multisegmental stenosis of the left main bronchus causing partial left lung atelectasis (bronchus intermedius is also narrowed laterally). Note the thickening of the narrowed bronchial wall, suggesting granulomatous infiltration

Kidney and Urologic Manifestations

Kidney

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) granular 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's syndrome) and systemic lupus erythematosus. 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) [44].

Rarer renal manifestations include granulomatous nephritis, interstitial granulomatous renal masses and aneurysms of the branches of the renal arteries, including their intraparenchymal portions [45, 46]. A possible (but low) increase in frequency of kidney cancer has been suggested by some studies or case reports, but most were probably related to bladder-toxic treatments [47].

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 [46]. Granulomatous prostatis, ischemic and/or granulomatous orchitis, and penile ulcers have been reported [46]. Vulvar ulcerations have been reported in women.

Bladder involvement is rare, and inflammation and/or hematuria originating from the bladder should suggest infection and/or hemorrhagic cystitis in patients receiving cyclophosphamide and bladder cancer in those who received cyclophosphamide and/or heavy smokers [48, 49].

Neurologic Manifestations

Peripheral Nervous System Manifestations

The peripheral nervous system is affected in 11–68 % of patients [50, 51]. Clinically, (asymmetrical and asynchronous) mononeuritis multiplex represents the principal pattern of peripheral nervous system involvement (45–79 % of cases), most frequently involving ulnar and peroneal nerves, followed by sensorimotor (symmetrical) polyneuropathy, both related to axonal ischemia due to vasculitis of the vasa nervorum of the small epineural vessels [50].

Central Nervous System Manifestations

The central nervous system is involved more rarely, in 6–13 % of patients, and often later and more progressively (except for the exceptional strokes) than the PNS [52]. Central nervous system involvement can result from extension of sinusal 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 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 usually due to compression by a meningeal granulomatous infiltrate rather than spinal cord ischemic vasculitis [53]. 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 due to compression by extensive meningeal or pseudotumoral intraorbital lesions or, more rarely, nerve ischemia and/or inflammation.

Skin and Oral Mucosal Manifestations

In total, 10–50 % of patients show skin lesions, primarily palpable purpura (Fig. 9.10). Macules, papules, ulcers, digital gangrene or, more rarely, subcutaneous nodules can occur [54]. Involvement of the elbows and hands, including dorsal face and digital pulps, is common. Lesions can sometimes mimic erythema elevatum diutinum or pyoderma gangrenosum, which can also occur as a complication or an associated condition.

Skin biopsies most often reveal nonspecific perivascular infiltrates and/or aspects of leukocytoclastic vasculitis of small vessels, which is 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 [55].

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 [54]. Infiltrations of parotid and/or accessory salivary glands have been described.

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 pseudotumor or from ear, nose and throat and/or meningeal lesions (Fig. 9.11).

Conjunctivitis and episcleritis are relatively common and benign. Inflammation of the lacrimal gland (dacryocystitis) is also common and leads to a dry-eye sensation, watery eyes, or suprainfection because of clogged tear ducts, which may require surgical debridement procedure and/or stenting. Corneal ulcers and necrotizing nodular scleritis are more of a concern because of risk of eye perforation, loss of vision and endophthalmitis. Retinal vasculitis is rarer but can also cause blindness [56]. Extensive xanthelasma has been reported, especially after the regression of an orbital pseudotumor [54].

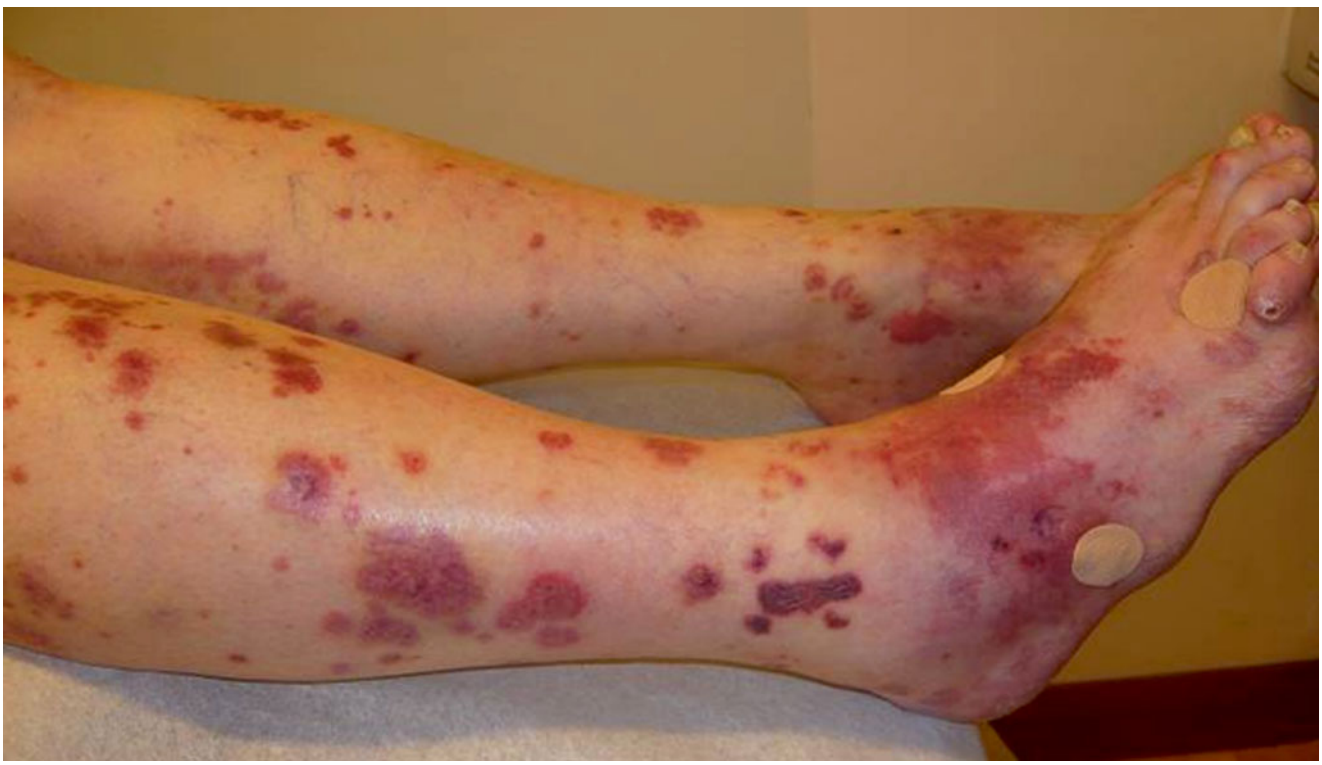

Fig. 9.10 Diffuse ecchymotic, necrotic and purpuric lesions in a patient with granulomatosis with polyangiitis (Wegener)

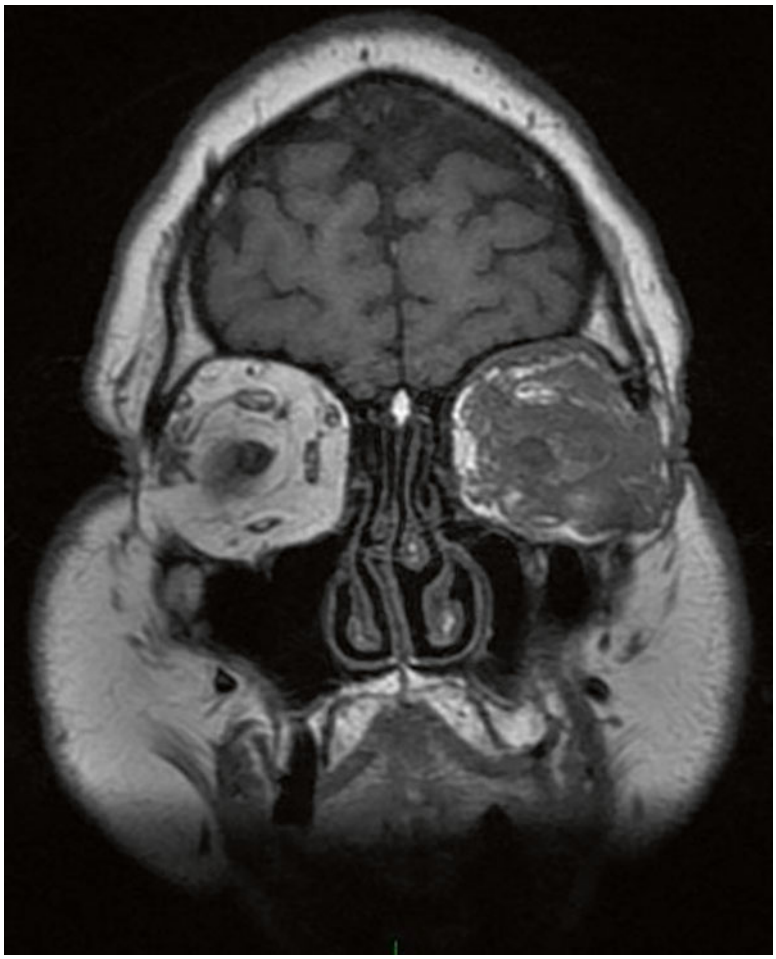

Fig. 9.11 Sinus and orbital CT scan (coronal) in a patient with granulomatosis with polyangiitis (Wegener). Massive infiltration of the left orbital cavity by a tumoral tissue (likely granulomatous on biopsy and exerting compression on eye and ocular muscles)

Cardiac Involvement

Cardiac involvement is rare (about 10 % of patients but up to 30 % in an autopsy series) [57]. MRI or sophisticated echocardiography (such as 2-D speckle-tracking) of the heart or electrophysiologic investigations can reveal subclinical abnormalities, whose prognostic value remain to be determined [58].

Sinus tachycardia is common during the active phases of the disease, as are arrhythmias, especially atrial fibrillation. Conduction disorders due to granulomatous infiltration of cardiac conductive tissue can lead to atrioventricular block or 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 silent clinically, 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 [59].

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 [60]. 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 risk.

The involvement of the appendix or pancreas (sometimes with challenging tumoral presentation) and/or gallbladder has been reported. 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 non-traumatic rupture. Hepatic artery aneurysms, which can rupture, have been reported.

Gynecologic and Obstetric Manifestations

Few cases of mastitis have been described but can present as breast masses or ulcerated skin lesions. Uterine, adnexal 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 [61]. Decreased fertility resulting from the disease itself is possible, but overt ovarian involvement has rarely been described. Measurement of 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 flare or worsening during pregnancy post-partum or -abortion [62], 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 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 flare 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 favourable, perhaps with a slightly higher frequency of preterm deliveries [62].

Venous Thrombosis and Other Vascular Events

A few studies have reproducibly demonstrated an increased risk of venous thromboembolic events (phlebitis and/or pulmonary embolism) with GPA, mainly during active phases of the disease [63, 64]. 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 [64]. 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 cANCA may cross-react with plasminogen in certain conditions) [65].

Besides digital ischemia, stroke and/or coronary artery involvement, limb ischemia or carotid artery thromboses can occur, although rarely. A few cases of ascending aorta inflammation (aortitis), pseudo-tumor (periaortitis), or aneurysms of the aorta, subclavian arteries, popliteal, renal, hepatic and/or spleen have been reported. There is also a 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 corticosteroids [66].

Other Manifestations

Other rare manifestations include periosteitis, almost exclusively of the tibia, or pre-vertebral dorsal lesions, which can mimic fibrosing mediastinitis but are usually not erosive or compressive [67, 68]. Retroperitoneal fibrosis is exceptional.

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

Limited/Localized Versus Severe/Diffuse/Systemic Forms

Despite variation in definitions among studies and authors (Table 9.3), GPA can be differentiated into two 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 [17, 69–71]. 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 vs. 50 years old at diagnosis). ANCA are found in more than 90 % of patients with systemic/diffuse/severe GPA but only 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) [72, 73].

Pediatric GPA

GPA is rare in children. Clinical manifestations are similar to that for adults, but girls are more frequently affected than are boys, and nasal deformities and subglottic stenosis are more frequent [74] (Table 9.4). Kidney damage is also frequent and often with poorer prognosis than in adults. Venous thrombosis may also occur more frequently (up to 16 % of children with GPA). In contrast, neurological manifestations

Table 9.3 Definitions of forms of granulomatosis with polyangiitis (Wegener)

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

Adapted from Hellmich et al. [67]
EUVAS European Vasculitis study group, *VCRC* Vasculitis Clinical Research Consortium, *WGET* Wegener-Etanercept trial

Table 9.4 EULAR/PRINTO/PreS criteria and classification definition of granulomatosis with polyangiitis (Wegener) in children, Ankara 2008

Children GPA is a systemic inflammatory disease characterised 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, Necrotising pauci-immune glomerulonephritis

Adapted from Ozen et al. [74]
EULAR European League Against Rheumatism, *PRES* Paediatric Rheumatology European Society, *PRINTO* Paediatric Rheumatology International Trials Organisation

seem less frequent (18 % of cases) [75]. However, the overall prognosis is similar but with significant morbidity because of damage from disease and treatment side effects.

Diagnosis

Diagnostic Approach

Classification criteria have been defined (Table 9.1 for adults and Table 9.4 for children) but not diagnostic criteria. Efforts are ongoing internationally to revise existing classification criteria and, if possible, devise diagnostic ones. However, diagnosis of GPA is relatively simple in patients with typical clinical features (Box 9.1) 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. The presence of antiPR3 cANCA will almost definitively support the diagnosis, without the need for biopsy. However, even in this setting, as well as in less obvious ones, histological confirmation may be necessary. Renal biopsy in the setting of renal impairment may also provide prognostic information for renal recovery [44]. In addition, several mimickers that must be ruled out include infections (mainly endocarditis) and cocaine use, which can be both (transiently) associated with antiPR3 ANCA.

Box 9.1
Main diagnostic features of granulomatosis with polyangiitis (GPA; Wegener's granulomatosis) – *there is presently no official and validated set of diagnostic criteria*

Non-specific 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 sediment (also in other small vessel vasculitides), 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
Eye lesions: scleritis, dacrocystitis, retinal involvement
Laboratory investigations to support the diagnosis
Detection of serum ANCA (mainly, but not always and not exclusively, antiPR3 cANCA) in (50–75 % of the patients with limited GPA, and 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 (diagnostic yield varies depending on which organ is biopsied – highest for open lung biopsies, lowest for nasal mucosa biopsies)

Clinical Vignette

Four years earlier, a 50-year old female was hospitalized for severe anemia. She presented with dyspnea and initial laboratory tests revealed hemoglobin of 6.5 g/dL. She was having recurrent episodes of sinus and ear pain for the prior 6 months and intermittent nose bleeds. On exam, she had a nasal ulcer and bilateral chest rales. Her urine sediment analysis revealed microscopic hematuria and several red blood cell casts. Serum creatinine was 2.0 mg/dL (176 µmol/l), erythrocyte sedimentation rate was 78 mm/h. A chest computed tomography showed bilateral lung infiltrates and further tests revealed a positive anti-neutrophil cytoplasmic antibodies (ANCA) against proteinase 3 (PR3). A diagnosis of granulomatosis with polyangiitis (GPA – former Wegener's granulomatosis) was made and treatment with cyclophosphamide and corticosteroid was initiated. Patient had excellent response to therapy and 4 months later, cyclophosphamide was switched to azathioprine. Her serum creatinine at that time was 1.0 mg/dL (88 µmol/l). Corticosteroid dose was slowly decreased over a year and discontinued. Patient remained asymptomatic for 2 years, and azathioprine was stopped.

She now presents for a routine follow-up visit. She is not taking any medications. She has polyarthralgias, bloody-tinged rhinorrhea, dry cough and bilateral ear fullness. Her serum hemoglobin is 12 g/dL and serum creatinine is 2.5 mg/dL (221 µmol/l). A diagnosis of GPA relapse is suspected.

Laboratory Investigations

Biology

Nonspecific inflammatory syndrome is common at diagnosis and during disease flare, with increased neutrophil count, normochromic normocytic anemia (50–73 % of patients, usually worse in patients with alveolar hemorrhage) and thrombocytosis (30–65 %) [4]. Eryrthocyte sedimentation rate in the first hour and C-reactive protein level are increased in almost every patient with active disease [76].

Transient and moderate eosinophilia can occur, in less than 12 % of patients and rarely above 2,000/mm^3, sometimes with concomitant increase in serum IgE level. High levels of IgE and/or atypical findings, including asthma, should suggest eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome). Moderate lymphopenia, 700–750/mm^3, is common at diagnosis (and during active disease) but can also result from and/or be induced by corticosteroid therapy [77].

Routine laboratory tests should systematically be part of the initial work-up and monitoring during the disease course. Analysis of fresh urine sediment is important for all patients for detecting erythrocyte casts, which are more suggestive of glomerular disease than a tubular or interstitial condition.

Immunology

The detection of cANCA (by indirect immunofluorescence) with antiPR3 (by ELISA) is a major tool in diagnosis. Other detection techniques have been developed, that may yield faster results and/or a better sensitivity [78]. However, the frequency is lower in patients with limited GPA (50–75 %)

than generalized GPA (80–90 %). The prognostic value of ANCA and clinical utility of serial monitoring during treatment and thereafter are low and therefore should not dictate treatment adjustment.

Importantly, ANCA (and antiPR3 cANCA) may 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 (Churg–Strauss syndrome)) can have PR3-ANCA rather than MPO-ANCA, 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 cANCA with various ELISA results (antiMPO, antiPR3 antibodies, both or neither, with ANCA directed toward different antigens such as elastase) [79]. Patients with associated inflammatory bowel disease, chronic liver diseases (chronic hepatitis C or auto-immune liver diseases) or certain infections (endocarditis, fungal infection, tuberculosis) can also show low and, usually, transient titers of ANCA (and/or other auto-antibodies).

In addition, patients with high ANCA titers can test positive, usually transiently, for other auto-antibodies. 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 antiGBM antibodies. An association of the two antibodies can occur in a few (<5 %) patients with pulmonary–renal syndrome, who have worse global and renal prognosis than patients with only one of the two autoantibodies [80].

Radiology, Endoscopy and Other Non-biologic Investigations

Imaging of the chest and sinuses must always be performed, ideally with CT scans. Other radiological investigations (MRI or angio-MRI, cerebral angiography, ultrasonography or CT scan of the abdomen and pelvis) should be performed depending on clinical findings. The indication for endoscopy is guided by clinical manifestations. 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 [81].

Nasal fiberoscopy can be useful in patients with ear, nose or throat manifestations but is cautioned in patients with subglottic stenosis (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 infection (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 [4, 42]. 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 but also in the stomach or esophagus. Gastrointestinal biopsy incurs some risk (i.e., perforation) in these patients and the sensitivity is low.

Patients with peripheral neurologic symptoms, especially when subtle and non-specific as tingling in fingers, should undergo electromyography to confirm or exclude peripheral neuropathy. Subclinical nerve involvement can been seen and may dictate more aggressive treatment [51]. Electromyography results may also guide muscle and nerve biopsy, when considered. Many patients have transmission (up to 33 % of patients) and/or neurosensory perception (47 %) hypoacousia, which ideally can be quantified on audiography.

Pathology

GPA affects small-sized vessels, capillaries and sometimes venules, less commonly medium-sized vessels, and rarely large-sized ones (aorta). Therefore, biopsies of affected organs can help support the diagnosis and reveal vessel wall infiltration, mainly by neutrophils and lymphocytes (sometimes also with some eosinophils), fibrinoid necrosis and/or poorly formed granuloma, sometimes with palisading organization and/or giant cells. The co-existence of these three histologic aspects may be considered very suggestive of the diagnosis, but they are not always present in the same sample. The decision to obtain histologic diagnosis must be balanced with the risk of the biopsy itself, especially when the clinical features are suggestive of GPA and with antiPR3 cANCA.

Several biopsies are easy to perform, including skin and ear, nose and throat ones. Biopsies of skin lesions often reveal nonspecific leukocytoclastic vasculitis. Some other

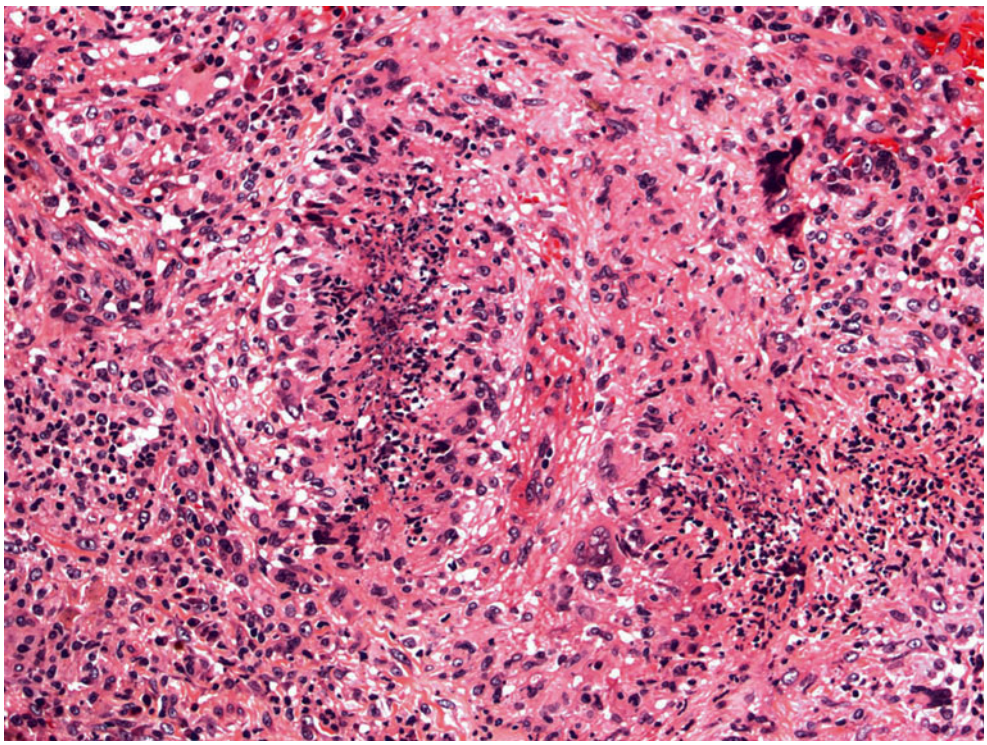

Fig. 9.12 Lung biopsy in a patient with granulomatosis with polyangiitis (Wegener). Histiocytes line a microabscess with central basophilic necrosis involving small artery (center); scattered giants (upper and lower right) are also present. (Hematoxylin and eosin; 100×) (Courtesy of Dr. Carol Farver – Cleveland Clinic, OH)

aspects are a little more (but not totally) specific, as in the presence of extravascular poorly formed granulomas and 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 nasal biopsies contribute to diagnosis [41]).

Tracheal biopsies, in patients with subglottic stenosis, can be hazardous, are often superficial and therefore are not very sensitive or helpful in clinical practice (<18 % show some histologic 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 % [82]. However, open-lung biopsies showed vasculitis and necrosis in 89 % of cases, granulomas and necrosis in 90 % and all three features in 91 % (Fig. 9.12). ENT and lung biopsies may also be very helpful to rule out infections, especially fungal infections (using different and specific staining methods).

Renal biopsy (in patients with renal involvement) typically shows pauci-immune glomerulonephritis (little or no immunoglobulin and complement deposition), also called necrotizing crescentic glomerulonephritis. Granulomas can be observed in up to 20 % of patients. The extent of lesions is associated with renal recovery after treatment [44]. Focal glomerular lesions (>50 % of normal glomeruli) and crescentric categories (crescent in >50 % of the glomeruli) have better prognosis than sclerotic (>50 % of glomeruli) or mixed categories.

Muscle and/or neuromuscular biopsies (mainly including the branches of the peroneal nerve) can show vasculitic features in up to 60 % of patients with clinical symptoms of peripheral neuropathy but are rarely necessary for 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 cases of headache can be considered; temporal artery involvement has been described [83].

Differential Diagnosis

The main differential diagnoses of GPA are in Table 9.5. Besides other systemic vasculitides, primary or secondary to other systemic diseases, granulomatous diseases (sarcoidosis, Liebow's lymphomatoid granulomatosis, beryllium disease, Crohn's disease), certain 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

Table 9.5 Main differential diagnoses of granulomatosis with polyangiitis (Wegener's granulomatosis)

Other vasculitides	
Primary	Microscopic polyangiitis
	Eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome)
	Polyarteritis nodosa
	Giant cell arteritis
	IgA vasculitis (Henoch-Schonlein purpura)
	Other primary vasculitis
Secondary	Relapsing polychondritis
	Drug-induced vasculitis
	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	
	AntiGBM antibody disease (Goodpasture syndrome)*
	Post-streptococcal glomerulonephritis
	Systemic lupus erythematosus
Cancers and hemopathies	
	Lymphomas
	ENT cancers
	Lung cancer/metastases
Miscellanous	
	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 & throat, *GBM* glomerular basement membrane, *HLA* human leukocyte antigen, *TAP1* antigen peptide transporter 1
*Now considered as a primary vasculitis (cf. Table 9.1) [10]

erythematosus and antiGBM antibodies. However, one should keep in mind the possible association of the latter with GPA (patients with high titers of both ANCA and antiGBM antibodies). Saddle nose deformity, although very suggestive is neither specific of GPA. It can occur in relapsing polychondritis, sarcoidosis, T-cell/NK lymphoma (centrofacial angiocentric lymphoma), congenital syphilis or other acquired and eroding infections like mucormycosis or leprosy, or after nasal traumas. Cocaine-induced vasculopathy, especially when cocaine is tainted with levamisole, is another important differential for patients with multiple and necrotic skin and ENT eroding lesions, with nasal septum perforation. Some of them can be tested with positive cANCA or even antiPR3 ANCA. Other drugs, including propylthiouracil- or minocycline, can induce vasculitis or several vasculitic features, most of the time associated with atypical or antiMPO ANCA, rather than antiPR3 ANCA.

Disease Activity, Prognosis and Damage Scores

Various scores have been designed to monitor disease activity and assess damage, mainly 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 way 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 [84]. The BVAS/GPA (WG) was developed specifically for GPA [85]. The damage extent index (DEI) is a rarely used activity score and the result is also related to prognosis [86].

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 (Churg–Strauss syndrome) [87]. After a new analysis of the French Vasculitis Study Group database, the FFS was revised and can now be used for GPA [88]. Five factors, assessed at the initial diagnosis of GPA, are associated with poor prognosis: serum creatinine level ≥150 μmol/l, specific GPA-related cardiomyopathy, age >65 years, severe and specific GPA-related gastrointestinal involvement, and no ear, nose or throat manifestations The 5-year mortality with FFS = 0 is <10 and 60 % for FFS ≥2 [88]. This revised FFS is not an activity score to be repeatedly calculated during the course of the disease 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, which is more recent and comprehensive but takes longer to complete [89].

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 [90]. 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 [91].

Treatment

Without treatment, GPA is almost always fatal within 6–12 months [57]. Since the use of corticosteroids in the early 1960s for vasculitis and the introduction of corticosteroids 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 [4]. Patient outcomes have continued to improve, with most of the advances made in optimizing treatment strategies, mainly to limit treatment-related toxicity. A more recent and major advance was the demonstration that rituximab is equally effective as cyclophosphamide for remission, which increases the therapeutic armamentarium.

Treatment has two phases: induction therapy based on the combination of corticosteroids and a second immunosuppressive agent, then, once remission is achieved, maintenance therapy (to maintain remission).

Induction Treatment for Systemic/Severe/Generalized Forms

Corticosteroids

Corticosteroids can rapidly improve the symptoms and signs of active GPA, but if prescribed alone, they will barely induce and/or maintain remission [57]. The initial dose of corticosteroids is 1 mg/kg/day prednisone-equivalent, sometimes preceded by 1–3 boluses of methylprednisolone (7.5–15 mg/kg/day) [92]. After the first 2–4 weeks of treatment, the dose of corticosteroids is slowly reduced by about 10 % every 1–2 weeks to achieve a half-dose (0.5 mg/kg/day) at about the third month of treatment. The optimal duration of treatment with corticosteroids is still controversial. In the United States, some centers consider corticosteroids beyond 6–9 months of little benefit or even with increased risk of long-term toxicity [93, 94]. Most of the other centers prescribe corticosteroids for a longer duration but at low doses (5–10 mg/day) for 2 years or more. A recent analysis of several trials suggested that low-dose prednisone beyond 6 and 12 months may be associated with low risk of relapse [95].

Cyclophosphamide

The combination of corticosteroids and cyclophosphamide remains first-line standard treatment for severe GPA [96]. It induces remission in >80 % of patients [97]. Cyclophosphamide can be administered as intravenous "pulses" (boluses at regular intervals) or continuous (daily) oral tablets. Oral daily cyclophosphamide is prescribed at the initial dose of 2 mg/kg/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), then at 0.7 g/m^2 or 15 mg/kg every 3 weeks [97]. The dose of each pulse should not exceed 1,200 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 given over 3 days; i.e., 5 mg/kg/day for 3 consecutive days every 2 weeks for the first month then every 3 weeks). Proper hydration should be ensured during the administration of cyclophosphamide. If cyclophosphamide is given intravenously at >600 mg, mesna should also be prescribed to reduce the bladder toxicity with cyclophosphamide [49, 98]. The dose of 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.

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 than intravenous pulsed route and has been associated with increased frequency of neutropenia [99] and in some (but not all) studies, with infection [97]. The risk of infertility and/or late complications (i.e., cancers, mainly bladder cancer, but 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 routes in continuous induction (followed by azathioprine maintenance) suggested that oral continuous cyclophosphamide (i.e., eventually a higher cumulative dose, 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 %) [100].

Whatever the route of administration, the 2003 CYCAZAREM study showed that oral continuous cyclophosphamide could be stopped as soon as the patient achieved clinical remission (absence of clinical disease activity, confirmed by a BVAS score of 0), thus possibly after only 3 months [96]. Thereafter, therapy 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 [101]. 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 major risk of subsequent malignancies, as reported in earlier studies (bladder cancer or hematologic malignancy, particularly lymphoma with risk multiplied by 11 when the cyclophosphamide was prescribed for 12–24 months), is greatly reduced [4, 102].

Rituximab

Rituximab is a chimeric monoclonal anti-CD20 antibody and a cornerstone agent for treating lymphomas that was first tested in GPA for treating refractory disease. It has then been evaluated in two randomized trials (RAVE and RITUXVAS) as an alternative to cyclophosphamide and was officially approved in April 2011 by the US Food and Drug Administration for treating severe forms of GPA (and microscopic polyangiitis) in adults, combined with corticosteroids [30, 32]. In these two studies, rituximab was not inferior to cyclophosphamide in inducing remission at 6 months. Tolerance to rituximab appeared to be 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 remained the same in both arms [103].

The doses of rituximab used in these studies were 4 infusions of 375 mg/m^2 at 1-week intervals. The protocol used for rheumatoid arthritis – two infusions of 1 g, 2 weeks apart – may have comparable effectiveness. Neither the RAVE nor RITUXVAS trial involved maintenance therapy after the induction courses of rituximab, and longer follow-up is needed to assess the need (or not) of maintenance therapy in patients achieving remission with rituximab.

Therefore, the choice of cyclophosphamide or rituximab is based on several factors, including the patient's plans for pregnancy, comorbidities and the high cost of rituximab. Rituximab has been mostly limited to patients with contraindication to cyclophosphamide, those with frequent relapses and/or those who have 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 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. Reports on the use of rituximab in children with GPA are still limited. Other factors may influence the therapeutic choice. The response to rituximab appears to differ depending on the form of the disease, with poorer and/or slower response for granulomatous than vasculitic manifestations [104]. 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.

Maintenance Therapy for Systemic/Severe/Generalized Forms

Maintenance therapy follows induction therapy once significant improvement or remission is achieved. The continuation of oral cyclophosphamide in early studies found a relapse rate as low as 13 % at 5 years [97]. Continuing intravenous boluses of cyclophosphamide in gradually longer intervals was not as effective, with a relapse rate of about 60 % at 5 years [97, 105]. However, the cumulative toxicity of cyclophosphamide, given orally or intravenously, is high, and thus, use of this agent must remain limited to induction therapy. Other immunosuppressive agents have been found as effective as continuing oral cyclophosphamide in maintaining remission, with less toxicity.

After therapy induction with cyclophosphamide, maintenance therapy can be initiated as early as remission is achieved [96]. The choice of maintenance therapy is mainly azathioprine, commonly 2 mg/kg/day orally, or methotrexate, 0.3 mg/kg/week, orally or intramuscularly [96, 101, 106]. These treatments seem equally effective and safe, at least at 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). Both azathioprine and methotrexate can increase the risk of opportunistic infections and cause liver toxicity and/or myelosuppression. Lung hypersensitive pneumonia to methotrexate 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 increased risk of hematological toxicity [107]. A pharmacogenetic analysis has also been proposed for methotrexate but is not routinely performed [108]. Whatever the local practice, close laboratory monitoring is mandatory after the start of maintenance treatment.

Despite these two maintenance treatments, the relapse rate remains 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 49 % at 27 months and 42 % at 5 years [96, 101, 105, 109, 110]. Hence, efforts and studies have been conducted to attempt to identify more effective strategies. 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 in the leflunomide group was only 5 % at 2-year follow-up [111]. Leflunomide (at the standard dose of 20 mg/day, possibly increased to 30 or 40 mg/day after 3–6 months) could be an option for maintenance therapy in patients with intolerance to azathioprine or methotrexate. However, side effects were frequent and included respiratory infections, arthralgias, 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 % [112], but the following studies reported higher rates, up to 43–48 % [113]. The results of the European IMPROVE trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy, showed mycophenolate mofetil inferior to azathioprine: at 4 years, the relapse rate was 55 and 38 %, respectively [114].

The optimal duration of these maintenance treatments is still unknown. The results of the ongoing European REMAIN trial (4 years of maintenance therapy with azathioprine as compared with discontinuing therapy at 2 years) may provide some answers but may not be definitive as to whether long-term maintenance therapy is associated with low risk of relapse. Results of controlled trials agree that the total duration of treatment (induction + maintenance) must not be <18 months. As mentioned previously, corticosteroids should not be unduly prolonged, but maintaining low-dose corticosteroids of about 5 mg/day over an additional 6–12 months could reduce the risk of relapse [95].

The strategy for maintenance with remission achieved with rituximab is not yet defined. Some groups monitor B-cell or CD19+ CD20+ counts and give a repeat full course of rituximab in case of B-lymphocyte reconstitution; others treat clinical relapse only; others recommend maintenance infusions at regular intervals, every 4–12 months, according to varying regimens; and still others prefer to maintain an immunosuppressive agent, such as azathioprine or methotrexate [115, 116]. Some studies have reported that routine maintenance infusions of rituximab may reduce the relapse rate to 7 or 22 % at 2–3 years (as compared with >70 % at 2 years in a retrospective study of patients with refractory disease who achieved remission with rituximab and did not receive maintenance infusions of rituximab) [31, 116]. However, controlled studies are needed to evaluate this observation. MAINRITSAN (ClinicalTrials.gov NCT00748644) was a prospective study of the French Vasculitis Study Group, recently closed and that should help to better define the possible role and regimen of rituximab infusions for maintenance therapy (500 mg infusion of rituximab given at the time of remission, which was achieved with cyclophosphamide and high-dose corticosteroids, then at day 15, months 6, 12 and 18 were compared to azathioprine). The results should be published in late 2014 (preliminary results presented at the 2012 annual ACR meeting suggested a much lower relapse rate at month 28 in the rituximab arm) [117]. A similar international study (RITAZAREM) is now under way.

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. Corticosteroids alone can improve disease in half of such patients but are unlikely to achieve or sustain remission [71, 106]. Few patients have achieved treatment success with cotrimoxazole (at 2 tablets/day, double strength) alone or most often combined with corticosteroids [72, 73, 118]. 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 [119]. 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 [69]. The remission rate with corticosteroids and methotrex-

ate 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 cyclophosphamide arm (70 % versus 47 % at 18 months), which indicated the need for a longer methotrexate treatment duration (>12 months) if initially effective.

Other Treatments in GPA

Intravenous Immunoglobulins

Intravenous immunoglobulins have mainly been 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 often only transient and/or not sustained (the disease often recurs after their discontinuation) [120]. 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 their transient use for GPA patients with ongoing infection, pregnant and/or in 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 antiGBM antibody disease. However, the benefit of plasma exchange in such patients with ANCA vasculitis has not been formally demonstrated. An ongoing randomized international trial (PEXIVAS) should determine more clearly the use of plasma exchange for this population. A previous study of patients with severe renal impairment, defined as serum creatinine level > 500 µmol/l, 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 [121]. No benefit was observed in the subgroup of patients with pulmonary–renal syndrome, which contrasts with findings from two retrospective series on plasma exchange in alveolar hemorrhage.

Plasma exchange usually involves 7 sessions over 2 weeks (3 sessions per week for 2–3 weeks), possibly followed by 2 more sessions per week for 1–2 weeks. During each session, 60 ml/kg plasma is substituted with albumin at 4 % or 5 % and/or fresh frozen plasma in case of alveolar hemorrhage. Despite an increased risk of deep vein thrombosis during active GPA, the risk of thrombosis in a central venous catheter (whose insertion is sometimes necessary to perform plasma exchange) does not appear to be greater than with other conditions, at least in adults. In children, this risk may be greater.

Anti-TNF-α

Infliximab and etanercept, both TNF-α blockers, have been used in refractory ANCA vasculitis but are now seldomly used, despite some beneficial results with infliximab (at 5 mg/kg on days 0, 15, and 45 and then every 1–2 months) [122, 123]. The results of the WGET study on etanercept combined with conventional treatments have been disappointing: etanercept added no benefit in preventing relapse 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 corticosteroids and cyclophosphamide) and several years after the end of the study [124]. Thus, the use of anti-TNF-α is not recommended for GPA.

Cotrimoxazole

Chronic carriage of *Staphylococcus aureus* in the nostrils is considered a risk factor of GPA relapse [21]. Besides basic science evidence, as described previously (cf. Pathogenesis), this association has been suspected in practice since 1985 when the prescription of antibiotics, especially cotrimoxazole (trimethoprim-sulfamethoxazole), combined with other treatments, was found to provide better disease control and reduce the relapse rate [118]. However, cotrimoxazole (trimethoprim-sulfamethoxazole) cannot substitute for immunosuppressive maintenance, being clearly not as effective [119]. When given at a high dose (320 mg trimethoprim/day, sulfamethoxazole 1,600 mg/day), combined with or following the usual maintenance treatments of GPA, cotrimoxazole could further reduce the relapse rate by 40 % at 1 year, regardless of the presence or not of *S. aureus* on nasal swabs [21]. However, 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.

Importantly, cotrimoxazole must be prescribed for prophylaxis against *Pneumocystis jiroveci* pneumonia in patients with GPA (160 mg trimethoprim with sulfamethoxazole 80 mg every day or, alternatively, 320 mg trimethoprim and sulfamethoxazole 1,600 mg three times per week) [92]. The risk of *P. jiroveci* pneumonia is relatively small, but real in patients receiving cyclophosphamide combined with high-dose corticosteroids and probably exists with other induction agents such as rituximab. A low dose likely has no benefit in terms of preventing relapse or controlling manifestations. In case of allergy or intolerance to cotrimoxazole, prevention of pneumocystosis is based on aerosolized pentamidine (300 mg every 4 weeks), oral dapsone (100 mg/day, which can cause anemia hemolysis even without glucose-6-phosphate dehydrogenase deficit, or more rarely methemoglobinemia) or atovaquone (1,500 mg/day). None of these drugs has been studied in GPA or reported in anecdotal cases as being effective for GPA.

Specific Treatments for Certain Manifestations of GPA

GPA patients often need multiple other treatments, including dialysis for severe renal disease, surgery for intestinal perforation or gangrene of limb extremities, pacing for severe conduction disorders, and local treatment of episcleritis. Kidney transplant for patients with end-stage renal disease or surgical reconstruction of nasal deformity 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 control of other GPA manifestations. The response to systemic therapy, including corticosteroids, can be as low as 22–44 % [38, 39]. Response to cyclophosphamide or newer agents such as rituximab seems limited. Thus, local treatment based on (repeated) dilation with candles or balloons is often required, followed, at least for subglottic stenosis and main bronchi, by local injection of corticosteroids. Some groups also end the dilation session with local application of mitomycin. The use of lasers can lead to more adherent fibrous scars. 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 main bronchi, is hazardous and is not standardized.

Adjuvant Measures and Prevention of Treatment Adverse Effects

The 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 [125]. Potential adverse effects of prolonged corticosteroid therapy are numerous and require at least the prescription of calcium (500–1,000 mg/day), vitamin D (2,000–3,000 IU/day) and, often, bisphosphonates, according to updated recommendations by rheumatology societies. Prevention of opportunistic infection should remain a major facet of patient management. Besides cotrimoxazole to prevent pneumocystosis pneumoniae, annual vaccinations for influenza (flu) and 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 GPA onset or flare. Conversely, in patients receiving high-dose prednisone and potent immunosuppressants, the efficacy of most vaccines remains unpredictable [126, 127], 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 corticosteroid therapy in addition to specific pro-atherothrombotic complications associated with GPA [66]. The risk of late neoplasia induced by treatments must be considered in treatment decisions [48], 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 or worsening symptoms during treatment for GPA should always raise suspicions of an infection complication. In the rare case of a patient with disease truly refractory to corticosteroids and cyclophosphamide administered intravenously, a switch to continuous oral cyclophosphamide can be attempted [128]. In other cases, for patients with a contraindication to cyclophosphamide (e.g., allergic reactions, hemorrhagic cystitis, bladder tumor, cumulative dose >20–35 g) and/or who have experienced multiple relapses, other treatments should be given, especially rituximab. Patients with disease resistant to all of these treatments, administered at sufficient doses and recommended intervals and after excluding other conditions that can mimic vasculitis flare (cancer, infection), other strategies must be considered on a case-by-case basis and in collaboration with reference centers for vasculitis.

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 a repeat course of cyclophosphamide in patients with relapsing disease [30]. The cumulative dose of cyclophosphamide previously received must also be taken into account in choosing between these two immunosuppressive induction therapies. Conversely, cyclophosphamide should be considered for patients with limited GPA who have not received cyclophosphamide and did not achieve remission with a combination of corticosteroids and methotrexate, unless contra-indicated.

Treatments Under Investigation and/or Development

Intensive chemotherapy followed by autologous bone-marrow or stem-cell transplantation remain anecdotal therapy for

GPA and under investigation in few selected centers. Several molecules and biologics are being studied, such as CTLA4-Ig (abatacept), gusperimus (15-deoxyspergualin), alemtuzumab (antiCD52) or anti-C5 complement receptor antagonist (CCX168) [36, 129, 130]. A recent open-label study reported promising results with abatacept for relapsing or refractory limited disease [131], that need to be further confirmed with a prospective controlled study now. Other potential therapeutic targets are constantly being identified, considered or studied, such as IL-17, IL-23 or IL-6, but are all at very early stages of consideration.

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) [109]. The main causes of early mortality in recent studies are infections and poor disease control. After the first year post-diagnosis, the leading causes are cardiovascular complications, infections and late cancers [90, 132, 133].

As mentioned previously, five factors present at the time of initial diagnosis of the GPA are associated with poor prognosis: serum creatinine ≥150 µmol/l, specific cardiomyopathy, age >65 years, severe gastrointestinal involvement, and absence of ear, nose and throat involvement [88]. Previous or other studies have reported poor prognosis with renal failure (defined by serum creatinine level >160 µmol/l or glomerular filtration rate <15 ml/min) and/or age >50–52 years, whereas ear, nose and throat symptoms had a good prognostic value in terms of survival [90]. Pulmonary disease was identified as a poor prognostic factor in one study [110]. Although alveolar haemorrhage may be responsible for massive and acute respiratory distress syndrome, it has not been clearly identified as associated with poor prognosis with appropriate treatment. A recent analysis of patients from several trials of the European EUVAS group reported an increased risk of death, but not significant, in patients with alveolar haemorrhage (HR 1.35, 95 % CI 0.70–2.64) [134].

AntiMPO + GPA is rare but severe and associated with an increased mortality as compared with antiPR3+ GPA (which, in contrast, may be associated with increased risk of relapse) [90]. A high rate of antiPR3 cANCA at diagnosis (by immunocapture ELISA) has been associated with low survival rate, as well as anemia, because of inflammation, alveolar hemorrhage and/or renal failure [90].

Relapse

The high risk of relapse, sometimes on multiple occasions in the same patient, is a hallmark of GPA. The risk of relapse is high in patients not receiving maintenance therapy. However, even with maintenance therapy, relapse remains frequent. The rate of relapse-free survival does not exceed 42–57 % at 5 years with current conventional treatments, although it has improved in recent decades [105, 109].

Relapse may occur more frequently with antiPR3 than antiMPO ANCA [135–137]. However, the predictive value of monitoring ANCA titers during treatment is controversial. To date, the serial measurement of ANCA should not be used to dictate treatment adjustment. The persistence of ANCA titers during treatment, especially when switching to maintenance therapy, was found 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 [138]. However, these results emphasize that relapses are not systematic, even with persistent ANCA positivity [139]. Conversely, relapses can occur in patients negative for ANCA [140]. 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) [141]. The magnitude of the increase in ANCA titers was thought to improve the predictive value of this factor, with a relative risk of relapse of 14.5 with ANCA titers increased by more than 4 times the previous value [139]. However, 18–43 % of patients with increased cANCA titers on immunofluorescence and 29 % with increased antiPR3 titers on ELISA did not experience relapse [142]. One prospective study showed the rate of achieving remission not associated with decrease in antiPR3 ANCA titers and that subsequent increases did not predict relapse (HR 0.8, 95 % CI 0.4–1.9). Finally, a recent 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 treatment decisions [143].

Several other clinical factors have been identified as potentially predicting relapse in different patient cohorts. Standardized prospective studies are needed, as is, most importantly, determining whether treatment can (or should) be adjusted individually by the presence or not of these factors. The most reproducible factors are the presence of 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 dose of corticosteroids <20 mg/day before the third month), previous relapse, and pulmonary and/or ear, nose, and throat [135, 136, 141, 144] disease. 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 indeed suggest a greater association of relapse and 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 high mortality rate. A longer duration of low-dose corticosteroids (about 5 mg/day after 1 year post-diagnosis) may be associated with low risk of relapse, but this observation, as mentioned previously (cf. Treatment) remains controversial [93, 95].

Studies are under way to identify new and more useful biologic factors to help differentiate between infections and disease flares, assess disease activity and predict relapse, as are studies of cytokine profiles and genomic investigations [145].

Damage and Disease Burden on Quality of Life

Only 11–14 % of patients surviving GPA remain without any damage [146]. 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 deformity (23 %) [37]. 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 increasing patient survival [66]. 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 frequent relapses in survivors. With proper and prolonged treatment, patient survival exceeds 80 % at 5 years. Epidemiological and clinical trials are advancing diagnosis and treatment, adding to our understanding of the pathogenesis of the disease. New drugs have been developed over the past decade. Some, such as rituximab, are now part of the approved therapeutic armamentarium. New agents and drugs will certainly be developed. Optimal treatments to prevent ear, nose and throat erosive lesions and nasal deformities and to cure subglottic and bronchial stenoses and lingering ear, nose and throat symptoms are needed. Many other questions, even though seemingly simple, remain unanswered and include the optimal duration of maintenance treatment and the place of plasma exchange or combination therapies. Therapeutic trials have been and will continue to be conducted, on an international level, to further improve patient outcomes.

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Alveolar Hemorrhage

10

Jason Wells 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 10.1) and is associated with a number of histopathologic patterns. This chapter will review the approach to the diagnosis and the management of DAH.

Clinical Vignettes

Case One

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, recent 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

Table 10.1 Differential diagnosis of DAH based on pathology

Histology	Etiologies
Pulmonary Capillaritis	Granulomatosis with polyangitis
	Microscopic polyangitis
	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	Lymphangioleiomyomatosis
	Human immunodeficiency virus infection
	Pulmonary capillary hemoangiomatosis

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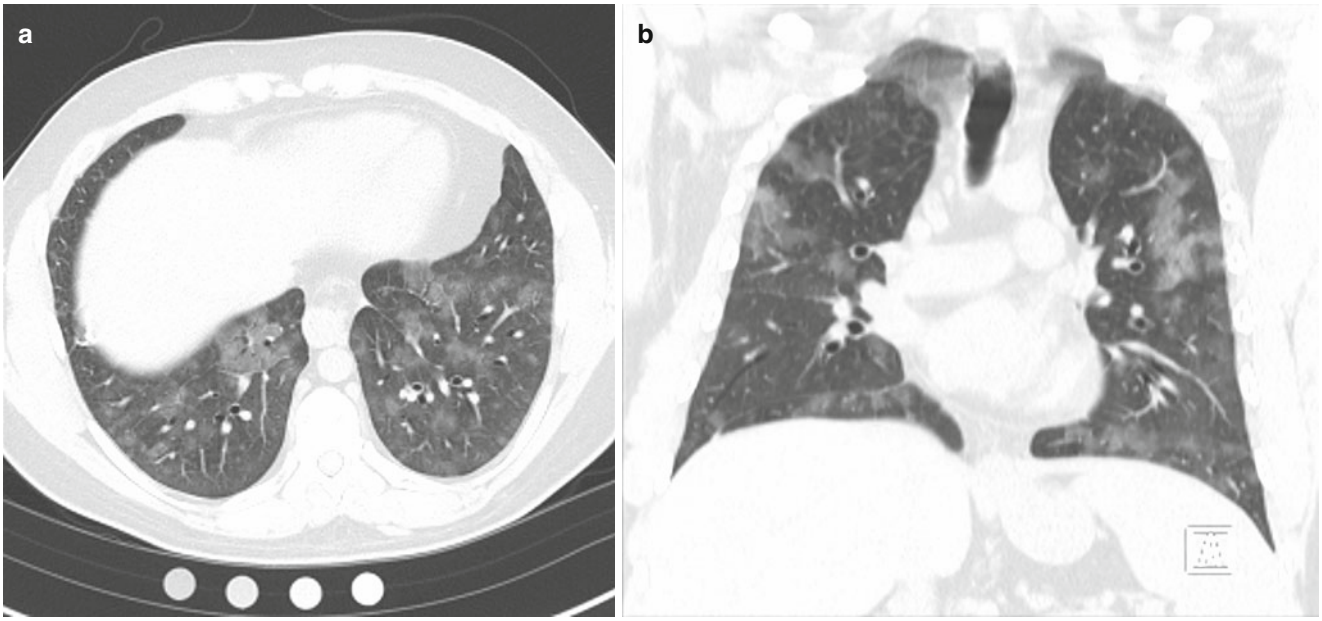

Fig. 10.1 (**a**, **b**) High resolution computed tomography images demonstrating patchy ground glass opacities consistent with alveolar hemorrhage

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-steroid 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 a positive guaiac test for occult blood. 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 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.

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

A 28 year old man presented to clinic for progressive dyspnea and fatigue. The patient has a complex past medical history notable for multiple episodes of deep venous thrombosis and a known diagnosis of anti-phospholipid 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 1/4–1/2 pack of cigarettes per day.

Physical examination was notable for a mildly elevated heart rate of 100 beats per minute and a mildly elevated respiratory rate of 20 breaths per minute. 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. 10.1a, b). Bronchoscopy revealed diffuse alveolar hemorrhage on lavage.

The patient was diagnosed with DAH secondary to recurrent anti-phospholipid 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 Three

The patient is 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 anti-nuclear 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.

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 per minute, 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 idiopathic pulmonary fibrosis (IPF) (Fig. 10.2a, b). White blood cell count was normal, but his hematocrit was reduced at 35 %. Bronchoscopy reveal diffuse alveolar hemorrhage (Fig. 10.2c). 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. Furthermore, the bronchoscopic finding of alveolar hemorrhage did not prove to represent clinically-significant hemorrhage and repeat serologies, ANCA testing, anti-basement membrane antibodies were all negative. Following a prolonged ICU course, he died of his respiratory failure.

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. anti-phospholipid 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, or they may present with fulminant disease including profound hypoxemia or respiratory failure. Constitutional symptoms may also commonly be 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

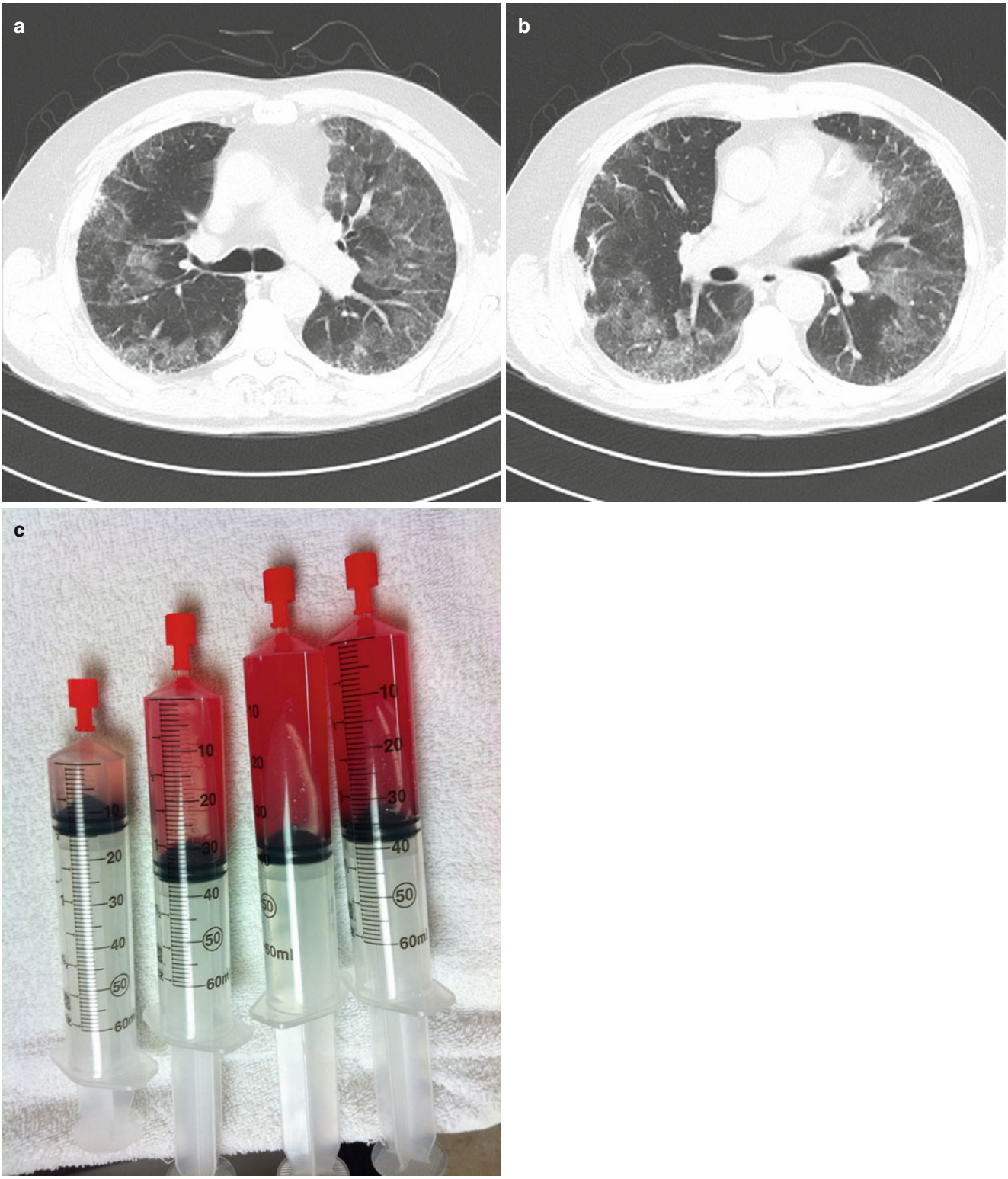

Fig. 10.2 (**a**, **b**)High resolution computed tomography images demonstrating patchy ground glass opacities superimposed on peripheral-predominant reticular infiltrates and early honeycomb changes. (**c**), Serial aliquots of bronchoalveolar lavage fluid demonstrating an increasingly hemorrhagic return diagnostic of alveolar hemorrhage

filling pressures? (3) Does the patient take any potentially causal medications such as penicillamine or propythiouracil? Or engage in illicit drug use, such as crack cocaine? (4) Does the patient have a coagulation disorder or take any anticoagulants that might contribute to hemorrhage?

Physical examination findings in DAH are nonspecific. 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 though 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, or 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 anti-phospholipid antibody syndrome (APLAS) [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 nonspecific 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 (i) proteinuria, (ii) microscopic (or gross) hematuria, ideally with dysmorphic, crenulated red blood cells, and (iii) 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 air space filling. 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, although 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 idiopathic pulmonary hemosiderosis or anti-phospholipid antibody syndrome as these patients may go on to develop obstructive and/or restrictive physiology.

Diagnosis (Table 10.1)

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 bronchus. 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 (Box 10.1). 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.

Box 10.1
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 should also be identified

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 Goodpasture's 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 anti-phospholipid antibody syndrome [1]. The presence of serum anti-neutrophil cytoplasmic antibodies (ANCA) and/or a positive anti-proteinase-3 or anti-myeloperoxidase enzyme-linked immuosorbant assay (ELISA) will assist with the diagnosis of a primary, small vessel, ANCA-associated vasculitis (AAV) such as granulomatosis with polyangiitis (the entity formerly known as Wegener's granulomatosis), microscopic polyangiitis, pauci-immune idiopathic pulmonary capillaritis, or Eosinophilic Granulomatosis with Polyangiitis (EGPA), the entity formerly known as Churg Strauss Syndrome [14]. In cases of DAH complicating SLE, the diagnosis of SLE is usually established [3]. 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's syndrome and scleroderma. Anti-streptolysin O testing is helpful in the identification of post-streptococcal disease, and 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. Furthermore, 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 or history 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 an invasive surgical thoracic 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 revealing 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 (i) capillaritis, (ii) bland hemorrhage and (iii) diffuse alveolar damage with hemorrhage, and the identification of the underlying histopathologic pattern can often be used to focus the differential diagnosis.

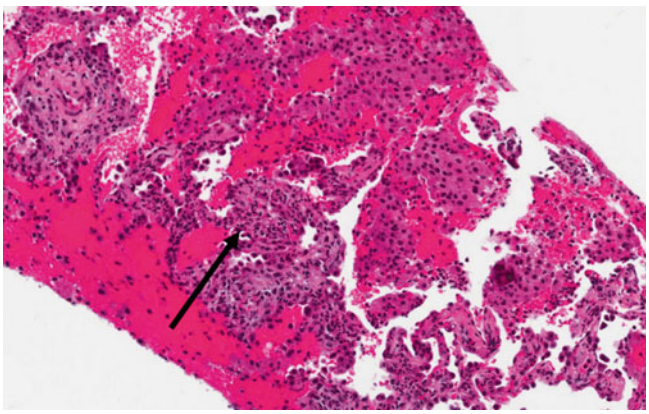

Fig. 10.3 Photomicrograph (20× magnification) of an H&E stained section showing lung parenchyma with diffuse airspace filling by hemorrhage and scattered macrophages. The *arrow* points to a region of capillaritis in which the alveolar septa are expanded by necrotic neutrophils and karyorrhexitic nuclear debris (Courtesy of Dr. Steven Groshong, Division of Pathology, Department of Medicine, National Jewish Health, Denver, Colorado, USA)

Pulmonary Capillaritis

Histology (Fig. 10.3)

Pulmonary capillaritis, also known as alveolar capillaritis, necrotizing alveolar capillaritis, and neutrophilic capillaritis, is one of the three core histologic pattern that may be associated with DAH. Pulmonary capillaritis is characterized by neutrophils infiltrating the alveolar septa along the pulmonary capillaries with associated nuclear debris 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].

Etiologies

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, 26].

As mentioned above, a diagnosis of MPA essentially requires that the patient have 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. Circulating immune complexes may be found in a significant minority of patients with MPA, but tissue localization of circulating immune complexes is rarely seen. ANCA are 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, 26, 27].

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 a 30 % mortality. For those patients who do survive, the 1-year and 5-year survival is reduced to 82 and 68 %, respectively [26, 28].

Treatment of DAH secondary to MPA is very similar to GPA and consists of supportive care elements plus glucocorticoids and plasmaphresis followed by 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 [29].

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 AAVand 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 to be used as such [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 diasthesis similarly addressed, treatment directed towards the underlying precipitating disease may begin.

Treatment of GPA requires the use of immunosuppressive agents (cytotoxic medications and systemic corticosteroids) that carry the risk of serious adverse side effects. As such, the intensity of the immunosuppresion 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]. 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 [23]. Dialysis-independent survival was greater in the plasma exchange group than the intravenous corticosteroid group such that the addition of plasma exchange to corticosteroids and cyclophosphamide has since been recommended for the management of patients with severe renal disease. Whether this same strategy may be applied to patients with DAH was tested in a 20 patient case series, and indeed, this strategy appears to be effective in diffuse alveolar hemorrhage as well [24].

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 cyclophosphamide [25]. No significant differences in total or serious adverse events were noted between the treatment groups. Subgroup analysis further showed that rituximab was equally effective with cyclophosphamide for the management of alveolar hemorrhage. Thus, rituximab may be used as a potential alternative to cyclophosphamide in severely ill patients, including those with DAH.

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 [30]. 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 [27, 31].

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. Co-morbid and/or precipitating infectious complications should excluded as a contributing factor to the DAH [3, 32, 33].

As with SLE itself, there is a strong female preponderance in DAH secondary to SLE, and patient are 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 50–90 %, 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, 33].

Treatment of DAH secondary to SLE includes the use of intravenous, high-dose methylprednisolone and cyclophosphamide. While plasmapharesis is also used for DAH complicating SLE, it is unclear whether or not this intervention provides additional benefit [27, 33].

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 APLAS 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, 34].

The management of APLAS is commonly complicated thromboemoblic disease and the need for anti-coagulation. When an episode of DAH occurs in a patient with an established diagnosis of APLAS, the presence of capillaritis and diffuse hemorrhage is further complicated 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 APLAS, including APLAS complicated by refractory DAH, have suggested that this agent may ultimately proven to have a role when more conventional therapies are unsuccessful [1, 34–36].

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 APLAS

(Asherson's 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, 35].

Goodpasture's Syndrome (Anti-basement Membrane Antibody Disease)

Goodpasture's Syndrome, or anti-basement membrane antibody disease, is an autoimmune disorder mediated by antibodies directed against the non-collagenous domain (NC1) of the alpha-3 chain of type IV collagen (and to a lesser degree the alpha-5 chain) found in basement membranes [37]. The majority of patients, approximately 60–80 %, present with a pulmonary-renal syndrome of diffuse alveolar hemorrhage 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 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, 37].

The clinical presentation of DAH due to ABMA disease is very similar to other cases of DAH of differing etiologies of DAH 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 [37]. Chest imaging studies, as with other cases of DAH, will show patchy diffuse alveolar infiltrates that appears 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 (ABMAs) 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 [37]. 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. 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 [38].

DAH associated with Goodpasture's is managed very similarly to DAH (or severe renal failure) secondary to GPA or MPA. Plasmapharesis combined with corticosteroids and a cytotoxic agent (i.e. cyclophosphamide) has been shown to be effective in both of these clinical contexts and is associated with improved mortality and renal recovery [39]. Early diagnosis and prompt institution of therapy is crucial to optimizing outcomes, and as such, it is sometimes necessary to initiate therapy pending a conclusive diagnosis. Ultimately, the similarities in therapeutic recommendations for pulmonary renal syndrome, whether it is due to ANCA associated vasculitis, SLE or Goodpasture's syndrome combined with the adverse effects associated with delays in therapy makes

this approach judicious. Steroids alone, or steroids combined with cytotoxic agents without the use of plasmaphresis do not achieve equivalent results. While there is no definitive data informing the optimal duration of plasmaphresis, the duration of therapy for Goodpasture's tends to be longer than in AAV, on the order of 10–14 exchanges, or until ABMAs become undetectable. With regard to choice of cytotoxic agent, cyclophosphamide is the most common agent utilized for life threatening alveolar hemorrhage. In more mild cases or as the patient's conditions improves, azathioprine (and more recently mycophenolate mofetil) have been used [20]. Lastly, rituximab has been proposed by some experts as a potential therapeutic agent for Goodpasture's syndrome based upon its mechanism of action and the pathogenetic role of ABMAs in the disease; however, beyond a handful of anecdotal reports, there is currently no evidence to support its use and its role in managing ABMA disease awaits further study.

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, 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 % [40]. 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 [37].

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 case of which were confirmed histopathologically on surgical lung biopsy [41]. 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-tranplantation capillaritis is identified, intensification of immunosuppressive regimen is recommended. Plasmapharesis has also been tried on a compassionate use basis, but remains unproven [42].

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/antisynthestase syndromes, and undifferentiated connective tissue diseases [31, 43]. 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 need not be present. Competing considerations include diffuse alveolar damage (i.e. acute interstitial pneumonitis 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, arthalgias 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 [44]. 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's disease or Behçet's 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 preferentially affects individuals of Middle Eastern origin, but is also

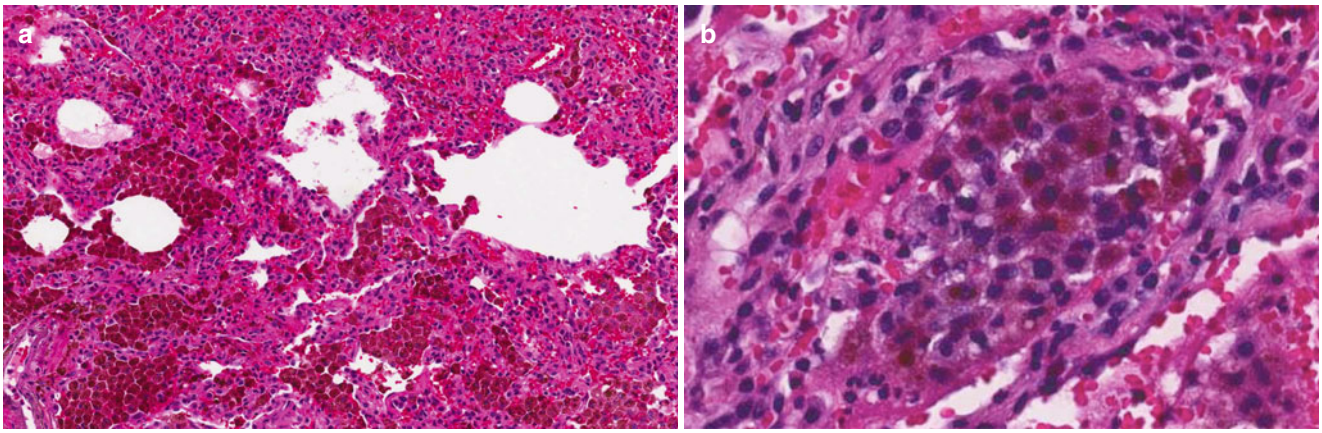

Fig. 10.4 (**a**) Photomicrograph (20× magnification) of a histopathologic section of lung demonstrating diffuse alveolar hemorrhage without features of capillaritis (bland hemorrhage). (**b**), Photomicrograph (60× magnification) of hemosiderin-laden macrophages filling the alveolar space (Courtesy of Dr. Steven Groshong, Division of Pathology, Department of Medicine, National Jewish Health, Denver, Colorado, USA)

found with increased incidence in Japanese populations. The most common pulmonary manifestation of Behçet's disease is pulmonary artery aneurysms, and these occur in 1–8 % of all individuals with Behçet's. 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 [45–47]. As with the other entities, management centers upon best supportive care combined with immunosuppressive therapy (corticosteroids and cytotoxic agents) [48].

DAH from pulmonary capillaritis has also been documented in mixed cryoglobulinemia. Mixed cryoglobulinemia is a small- to medium-sized vessel, immune complex and complement mediated vasculitis, and is 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 [49].

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 regards to inflammatory bowel disease, a number of pulmonary complications have been associated with both ulcerative colitis and Crohn's disease including bronchiolitis (panbronchiolits and bronchiolitis obliterans) bronchiectasis and interstitial lung diseases [50]. 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 [51].

Bland Pulmonary Hemorrhage (Fig. 10.4)

Histology

While both bland pulmonary hemorrhage and capillaritis show airspaces intra-alveolar filling by red blood cells, fibrin and hemosiderin-laden macrophages along with septal expansion be 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 demonstrated 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, 52].

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, 53].

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 [53]. 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 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, and at least at present, would still be considered IPH [54]. Similarly, subtle findings of capillaritis may easily be missed and cases of idiopathic pulmonary capillaritis may be mis-classified 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 [53]. 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 [53].

As with other cases of DAH, treatment of IPH begins with supportive care elements of oxygen, reversing any bleeding diasthesis, 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. Plasmapharesis 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, 53].

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, nitrofurantion, 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's disease, or primary biliary cirrhosis) [55, 56]. 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 [57, 58]. Pulmonary capillaritis has not been associated with pencillamine therapy. Treatment includes cessation of pencillamine plus corticosteroids, cytotoxic therapy and plasmapharesis [55].

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 [57, 58]. 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 [58]. 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 (i.e. chemotherapy), hemolytic uremic syndrome and disseminated intravascular coagulation may all lead to bland hemorrhage [4, 5]. Similarly, pharmacologic anticoagulation with vitamin K antagonists, fractionated or unfractionated heparin, direct thrombin inhibitors, IIb/IIIa inhibitors and fibrinolytic therapy may also lead to alveolar hemorrhage [59]. 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 [60]. 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. Treatment in these cases is directed at the underlying cardiovascular pathology.

Other

Inhalation of acid anhydrides and isocyanates have 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 [61, 62].

Extremely severe cases of obstructive sleep apneaand 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 [63].

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 corticsteroids), vasodilator therapy, and anti-coagulation have all been attempted [64, 65] (Fig. 10.5).

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 diagnosed with ARDS. Other etiologies of DAD include acute exacerbations of fibrosing interstitial lung diseases, acute lupus pneumonitis, bone marrow transplantation, and acute interstitial pneumonitis. While DAH is not considered "characteristic" of underlying DAD, DAH is clearly associated with underlying DAD. Histology in these cases will show a dominant lesion of DAD characterized by non-cardiogenic 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

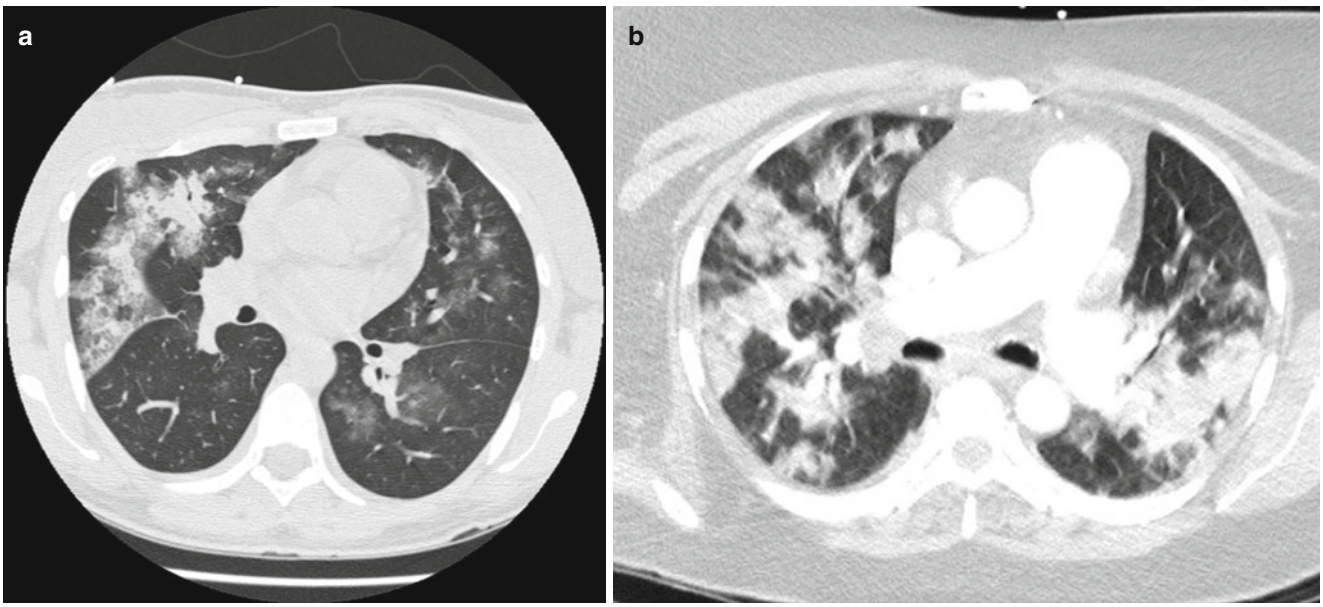

Fig. 10.5 (**a**) High resolution computed tomography image and (**b**), CT angiography image demonstrating a spectrum of disease associated with alveolar hemorrhage. Note that while both CT images demonstrate patchy alveolar filling patterns, the density of the infiltrates may range from ground glass 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)

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, 66]. In many ways, the presence of DAH in the setting of DAD is more confounder than clinically significant, and should not be mis-interpreted as being a major manifestation of DAD (Box 10.2).

Box 10.2
Entities Characterized by Prominent and Severe Diffuse Alveolar Hemorrhage

Entities
Granulomatosis with polyangitis
Microscopic polyangitis
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 noninfectious lung injury after HSCT or the idiopathic pneumonia syndrome (IPS) [67]. 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 regimens, and 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 [2].

Diffuse alveolar hemorrhage 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 is limited. Histology in "crack lung" is characterized by DAD, edema, inflammatory infiltrates, and hemorrhage. The mechanism of injury is believed to relate to profound vasocontriction of the pulmonary vascular bed and its resulting cellular damage. Additionally, 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.

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 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 incidence and pathophysiology remain largely unknown, and the diagnosis remains one of exclusion. By definition, AE-ILD is the presence of an acute respiratory decline (≤30 days) 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 no infection and no alternative cause of the decline can be identified [72].

Recently, two groups of investigators have reported their experience with this entity improving our understanding of the clinical features of AE-ILD. 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 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 %. Diffuse alveolar hemorrhage was noted as the cause of death in 2.2 % of patients. Predictors of poor outcome included older age, low FVC and DLCO, and immunosuppressive therapy [73].

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 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 [74].

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. Additionally, the ACE-IPF study of Anti-Coagulant Effectiveness in Idiopathic Pulmonary Fibrosis was stopped early due to an excess of mortality in the warfarin treatment arm. 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 [75]. 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. Unlike ARDS, symptoms tend to evolve over days to weeks (and in some reports, months) and include cough, dyspnea, fatigue, malaise, fever, and "flu-like" illness. Symptoms typically progress to include more marked dyspnea, hypoxemia and respiratory distress [76]. Imaging studies universally reveal bilateral infiltrates, and on more refined HRCT imaging, appear as ground-glass abnormalities and consolidation [77]. 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 [75].

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 [78]. 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 is lacking and is 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 1992 American European Consensus Conference criteria defined ARDS by the presence of (i) acute onset (≤7 days) respiratory failure, (ii) bilateral lung infiltrates, (iii) severe hypoxemia (PaO_2/FiO_2 ratio of <200) and (iv) the absence of evidence of left atrial hypertension (pulmonary capillary wedge pressure <18 mmHg) [79]. 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 (i) determining and treating the underlying cause of the lung injury and (ii) 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 (echocardiography, serial electrocardiography, cardiac enzymes). Bronchoscopy may be performed in patients in whom no obvious inciting etiology is identified. Mechanical ventilatory support is required in virtually all patients, and a lung protective ventilatory strategy is recommended in all ARDS patients (see below) [80, 81].

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

Mortality in ARDS has improved over the past 10–15 years 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 patient 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 [82]. Further investigation into ventilatory strategies using differing levels of positive end expiratory pressure were unable to achieve clinically significant differences, but re-inforced the desirability of keeping the end inspiratory plateau pressure below 30 mmHg [83]. 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 [84]. 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 % [81].

As the mortality in ARDS has improved, a new appreciation has developed for the long-term morbidity of survivors. Problems including persistent dyspnea, fatigue and exercise intolerance, restrictive lung disease, cognitive dysfunction, post-traumatic stress disorder, and neuromuscular weakness are increasingly recognized as important long term sequellae following an episode of ARDS [80].

Miscellaneous Causes

Etiologies

Human Immunodeficiency Virus (HIV)

Infection with HIV predisposes patients not only to its all to well known infectious complications, but also a broad array of non-infectious pulmonary complications such as Kaposi's sarcoma, interstitial lung disease (nonspecific 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 [85]. Independent risk factors for DAH in this study were (i) pulmonary Kaposi's sarcoma, (ii) hydrostatic pulmonary edema, (iii) cytomegalovirus pneumonia, and (iv) thrombocytopenia (platelets <60,000 cell per microliter). 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's).

Pulmonary Capillary Hemoangiomatosis

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.) [86] Given its rarity, no effective therapies have been identified. There is one case report of clinical improvement following treatment with interferon alpha-2a [87].

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, as has been discussed, 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 diffuse alveolar hemorrhage.

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. anti-phospholipid 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 is recommended. In general, non-invasive positive pressure ventilation would be contraindicated in any patient suffering respiratory failure secondary to active DAH. Still, to date, no randomized trials have been performed to determine the most effective mode of mechanical ventilation in DAH. As has been discussed previously, 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). Given the clinical similarities between DAH complicated by respiratory failure and ARDS, it is reasonable to extrapolate this data to the care of patients 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 is 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 [88]. 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's 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.

For patient's with suspected pulmonary capillaritis, in whom a diagnosis of GPA, MPA, SLE or Goodpasture's

syndrome is being 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 plasmaphresis is recommended along with the introduction of a cytotoxic agent (e.g. cyclophosphamide). The data informing these treatment recommendations are derived primarily from the AAV and Goodpasture's syndrome literature and have been discussed earlier. The optimal timing of the introduction of the cyclophosphamide or other cytotoxic agent in the critical care setting, especially in patients with concomitant infection and/or requiring mechanical ventilation remains subject to debate. For patients with lesser degrees of disease severity, not requiring mechanical ventilation and without significant 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 agent). However, these cases can often evolve rapidly and close serial observation is required. If patients demonstrate clinical deterioration, therapy may need to be escalated.

As was discussed earlier, two recently published 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 [25, 89]. Furthermore, specifically with the RAVE study, rituximab was found to be as effective as cyclophosphamide in patients with alveolar hemorrhage. 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 plasmapharesis 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 hemorrhage. Similarly, ECMO has been utilized at the case report level to prolong survival while allowing the above therapies to have an effect, but pragmatically, the pro-inflammatory cascade triggered by the ECMO circuit and the need for antithrombotic therapies during ECMO administration complicates its use in DAH.

Conclusions

Diffuse alveolar hemorrhage 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 permits 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

11

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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 11.1), and a set of criteria for childhood TA have been recently published [5].

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 the most infrequent form 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.

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Table 11.1 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 3 of these 6 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 90.5 % and a specificity of 97.8 %

BP blood pressure (systolic; difference between arms)

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. 11.1). 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 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/1st h, 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.

Clinical Features

The clinical course of TA is classically thought to progress through three distinct stages: first, an early phase with

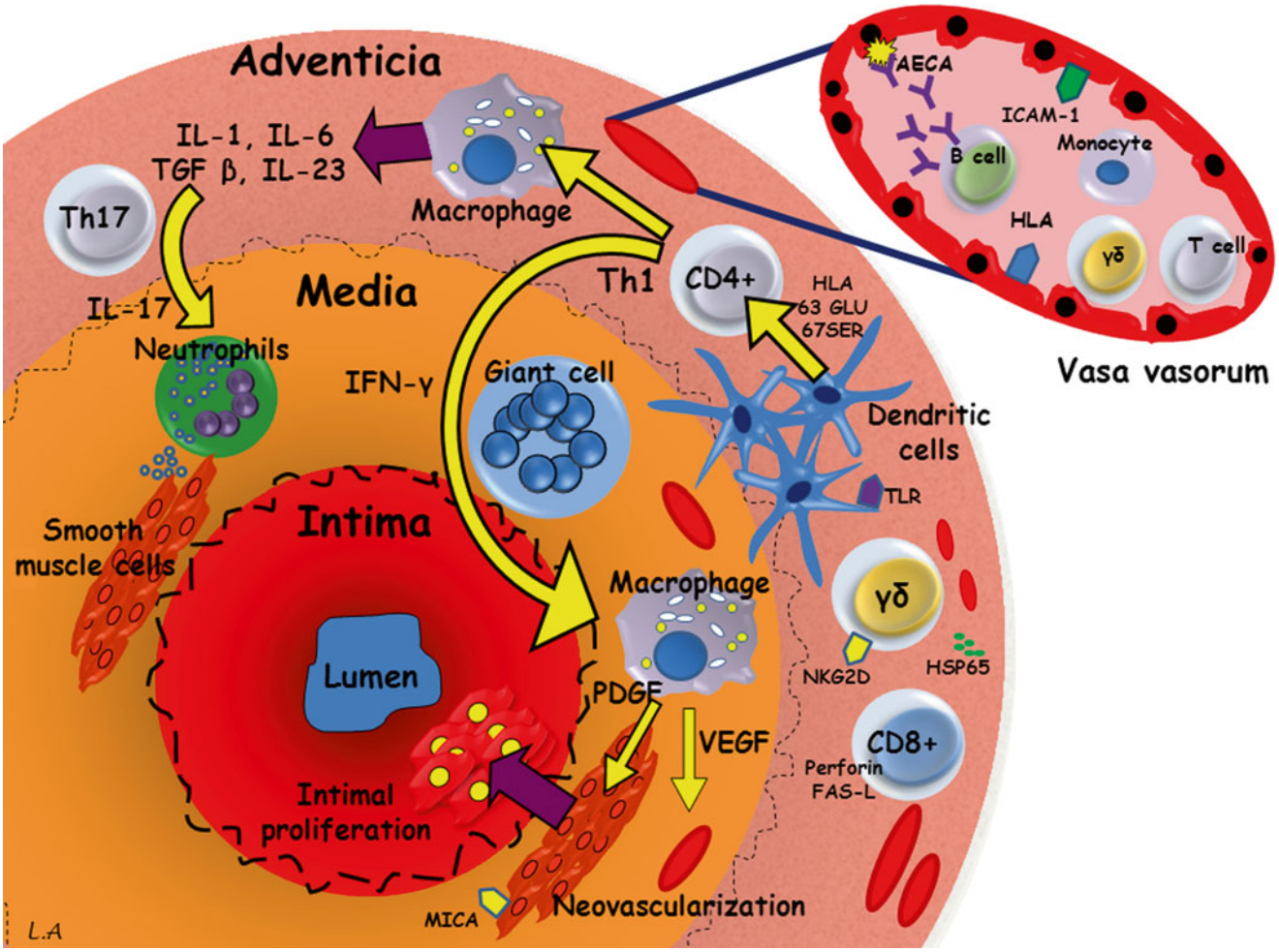

Fig. 11.1 Pathogenesis of Takayasu's arteritis. *AECA* anti-endothelial cell antibodies, *FAS-L* FAS ligand, *HLA* human leukocyte antigen, *HSP65* heat-shock protein 65, *ICAM-1* intercellular adhesion molecule 1, *IFN* interferon, *IL* interleukin, *TLR* toll-like receptors, *MICA* major histocompatibility 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

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 haemangiomatosis 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 11.2) are non-validated [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].

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. 11.2, 11.3 and 11.4). These latter offer several advantages, including their non-invasiveness 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 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

Table 11.2 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"

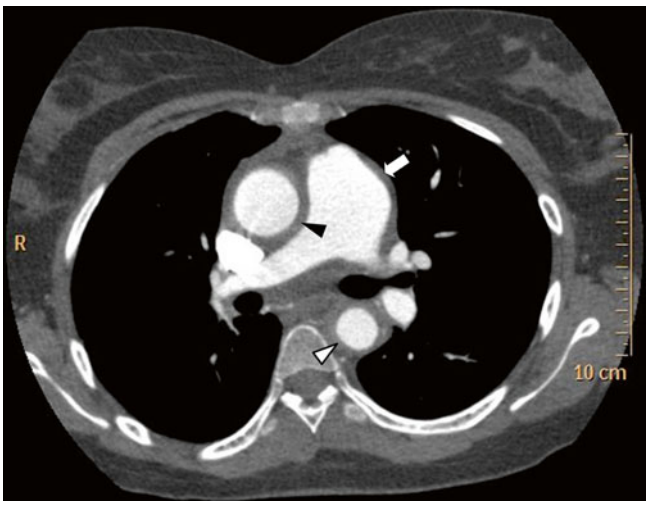

Fig. 11.2 Thoracic CT scan in Takayasu arteritis. Thoracic CT scan in mediastinal windows in an 18-year old woman with TA showing dilatation of the ascending aorta and increased thickening of the ascending aorta wall (*black arrowhead*), of the thoracic descending aorta wall (*white arrowhead*) as well as thickening and dilatation of pulmonary trunk (*white arrow*)

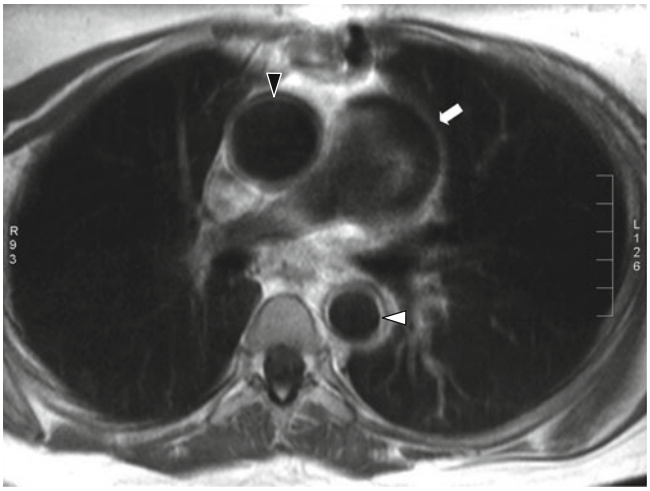

Fig. 11.3 Contrast-enhanced thoracic MRI in Takayasu arteritis. Contrast-enhanced T1-weighted black-blood thoracic MRI (axial view) in an 18-year old woman with TA showing dilatation of the ascending aorta and increased thickening of the ascending aorta wall with ring-like contrast enhancement (*black 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*)

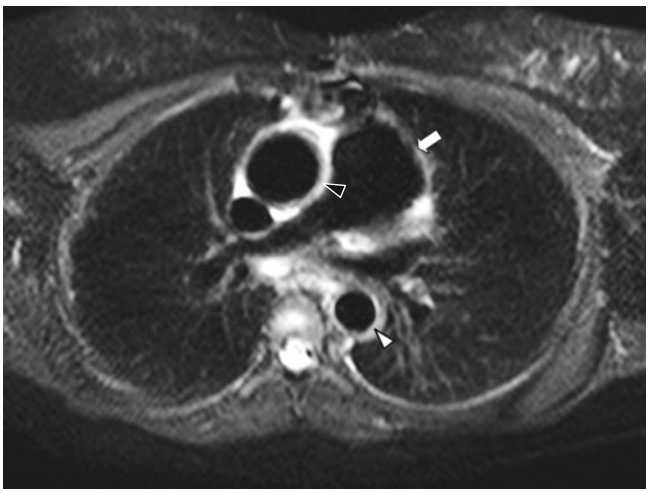

Fig. 11.4 STIR thoracic MRI in Takayasu arteritis. Short tau inversion recovery (STIR) thoracic MRI (axial view) in an 18-year old woman with TA showing dilatation of the ascending aorta and increased thickening of the ascending aorta wall with hyperintense signal (*black arrowhead*), and increased thickening of the thoracic descending aorta wall with hyperintense signal (*white arrowhead*) as well as thickening and dilatation of pulmonary trunk (*white arrow*)

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 6 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], cyclophosphamide [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 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 heat 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 *Streptoccocus 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 11.3) [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].

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, haemoptysis 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 haemoptysis (>500 cc) 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 Hugues-Stovin syndrome, which

Table 11.3 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

associates PAA and deep venous thrombosis [122]. It is still debated whether Hugues-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. Haemoptysis 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 haemorrhage 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 haemorrhage 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, haemorrhage 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 11.4. As mentioned before, it is still matter of debate whether Hugues-Stovin syndrome is an incomplete variant of BD or a distinct syndrome [123–125]. Hugues-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 11.4 Differential diagnosis of pulmonary arterial aneurysm

Inflammatory chronic disease
Behçet's disease
Hugues-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 500–1,000 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 embolisation should be preferred in case of massive or life-threatening haemoptysis. 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 use 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 therapy 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 haemoptysis 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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Pulmonary Vascular Manifestations of Hereditary Hemorrhagic Telangiectasia

12

Els M. de Gussem and Marie E. Faughnan

Abbreviations

ACVRL1	Activin-A type II like kinase 1
AVM	Arteriovenous malformation
BMP-9	Bone morphogenetic protein
BMPR2	BMP type II receptor
Eng	Endoglin
HHT	Hereditary Hemorrhagic Telangiectasia
HOCF	High-output cardiac failure
PAH	Pulmonary arterial hypertension
PH	Pulmonary hypertension
TGFBR2	TGF-ß type II receptor
TGF-ß	Transforming growth factor ß
VEGF	Vascular endothelial growth factor
VM	Vascular malformation

Clinical vignette 1

A 25 year old woman presents to the emergency room with sudden onset 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 37.1 °C and her oxygen saturation on pulse oximetry is 92 %. Mucocutaneous telangiectasia are visible on the lip and right index finger. Percussion of the left hemithorax is dull with corresponding decreased breath sounds. Chest-x-ray (Fig. 12.1a) reveals left sided pleural effusion with an obscured left hemi-diaphragm.

CT chest (Fig. 12.1b–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 labour 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. 12.2). On further history, the patient reports recurrent epistaxis since the age of 12. Family history reveals recurrent spontaneous epistaxis in the father, as well as stroke. The patient, and eventually her family, was thus diagnosed with Hereditary Hemorrhagic Telangiectasia (HHT).

Pulmonary Arteriovenous Malformations

Pulmonary AVMs are associated with underlying HHT in more than 80 % of patients [67]. Most other pulmonary AVMs are considered idiopathic [70] but they have also been very rarely reported in association with hepatopulmonary syndrome, schistosomiasis, mitral stenosis, trauma, actinomycosis, Fanconi's syndrome and metastatic thyroid carcinoma [33]. The detection of pulmonary AVMs, or their complications, may however predate the HHT diagnosis, particularly as HHT it is an under-recognized disorder.

HHT is an autosomal dominant disease, characterized by the presence of vascular malformations (telangiectasia and AVMs) and caused by mutation in either the *Endoglin* gene or the *ACVRL1* gene in 80 % of families. Pulmonary AVMs have a higher prevalence in patients with *Endoglin* mutation

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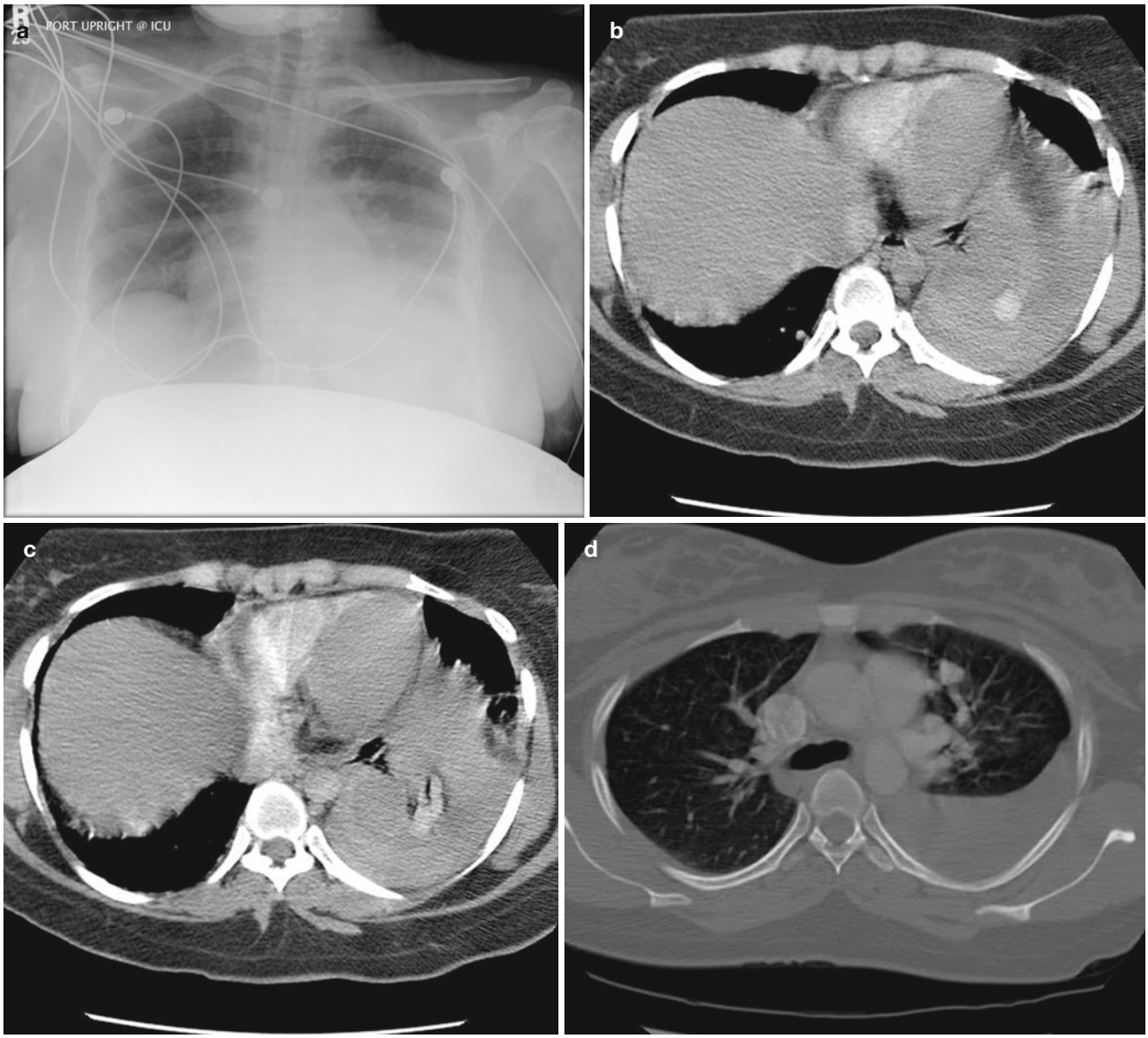

Fig. 12.1 (**a**) Case 1: Chest x-ray shows that the left diaphragm is obscured by a pleural effusion. The abdomen is protected by a lead shield. (**b–d**) Case 1: CT chest (selected images) showing that the left hemothorax and left-lower AVM (**b**, **c**) and left upper lobe AVM (**d**)

(49–75 %) than in patients with an *ACVRL1* mutation (5–44 %) [43, 45, 56]. These genes are involved in transforming growth factor- beta (TGF-ß) signaling pathway and though the disease is characterized by dysregulated angiogenesis, the exact pathophysiologic mechanisms of AVM development remains to be elucidated.

Most (80 %) pulmonary AVMs are simple fistulas consisting of a feeding artery directly connected to a draining vein, with only an intervening aneurysmal sac but no capillaries. About 20 % of pulmonary AVMs are complex with multiple feeding arteries, or have multiple draining veins or a septated aneurysmal sac [66]. A severe diffuse form of pulmonary AVMs is present in approximately 5 % of pulmonary AVM cases [22, 53].

Patients with pulmonary AVMs report exertional dyspnea, though only in approximately 50 % of patients. Less than 10 % present with classical features such as cyanosis, clubbing and pulmonary bruit. More typically, patients present with complications from pulmonary AVMs, such as massive hemorrhage or stroke. Hemorrhagic complications develop due to spontaneous rupture of a pulmonary AVM, leading to massive hemoptysis or hemothorax. This complication has occurred in 3–13 % of patients by the time of diagnosis of pulmonary AVMs. Even more frequently, patients develop neurologic complications, such as stroke, transient ischemic attack or cerebral abscess, with frequencies of 10–60 %, 6–47 % and 8–19 % respectively, by the time of diagnosis of pulmonary AVMs [17,

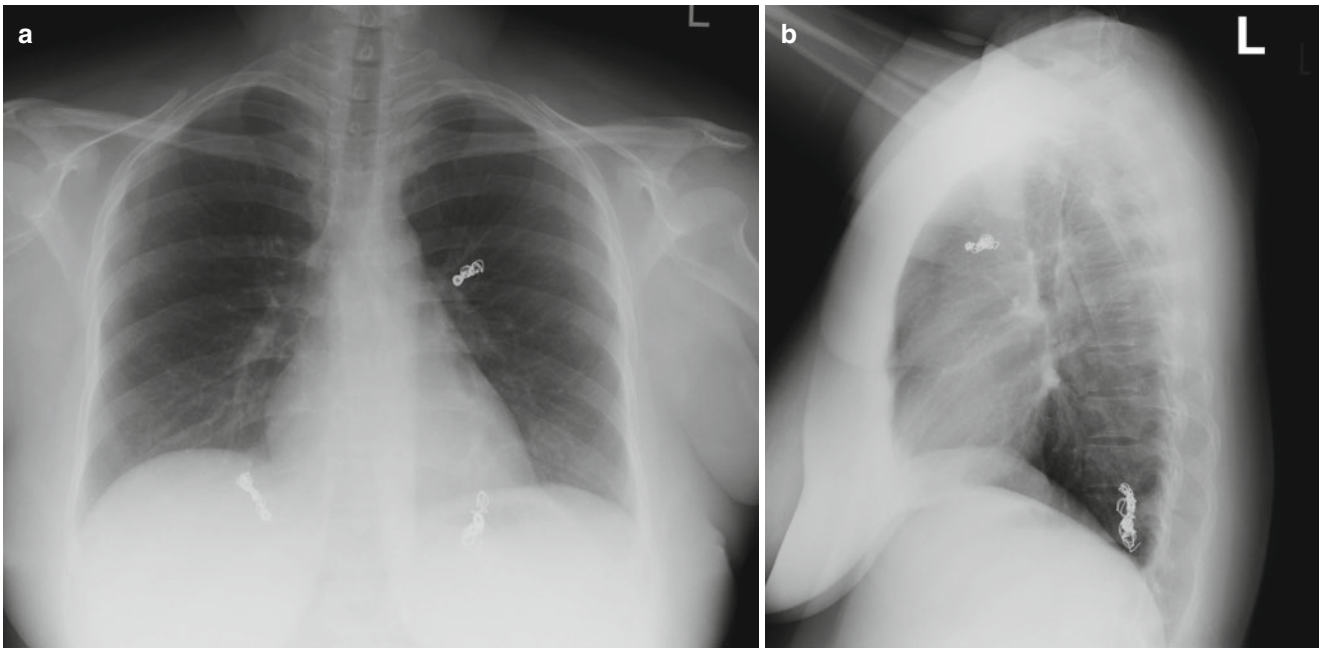

Fig. 12.2 (**a**, **b**) Case 1: Chest x-ray (PA and lateral) after embolization shows coils in the left upper lobe, left lower lobe and right lower lobe

51, 67]. The presumed mechanism for stroke is via paradoxical embolisation 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 are most commonly due to pathogens typical of periodontal source [49, 58, 60]. Interestingly, migraine is also frequently reported in HHT patients with pulmonary AVM, particularly with aura [54, 63]. 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.

Pulmonary AVM complications can be largely prevented, with appropriate screening and preventative therapy. The International HHT Guidelines [25], recommend screening all patients with HHT (or suspected HHT) for pulmonary AVMs, and treating preventatively. The recommended first-line screening test is transthoracic contrast echocardiography, with agitated saline, for the detection of right-to-left shunt. This is a low-risk and minimally invasive screening test, with a high sensitivity (93 %) and an excellent negative predictive value (99 %) for the presence of a pulmonary AVM [18, 65]. When there is evidence of right-to-left shunt on contrast echocardiography, CT chest is the recommended diagnostic test to confirm or rule out the presence of pulmonary AVMs [25], and this can be done without enhancement in most cases.

The degree of shunt on contrast echocardiography can be graded (1–4) according to the opacification of the left ventricle [4]. In case of a grade 1 shunt, there is minimal opacification of the left ventricle. In case of a grade 4 shunt there is extensive opacification of the left ventricle with outlining of the endocardium. The number of cardiac cycles after which contrast appears in the left ventricle is not predictive of an intracardiac or intrapulmonary shunt [72]. Increasing shunt grade is associated with increasing positive predictive value of the presence of AVMs requiring embolization [52, 65, 72].

Preventative transcatheter embolotherapy is recommended, by an experienced interventional radiologist, with the goal to occlude pulmonary AVMs with a feeding artery of 3 mm or greater (and in some cases those between 2 and 3 mm) [25]. Currently there are several devices being used for embolization, including various types of coils and also Amplatzer plugs. The reperfusion rates (mostly secondary to recanalization) with coils and Amplatzer plugs are similar, 7–10 % [44]. 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, with very rare angina pectoris, TIA, cerebral infarction [44, 48]. A migrating device mostly 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 after 1 year with a repeat unenhanced CT chest to confirm involution of the aneurysm and of the draining vein of the embolized AVMs [25]. If there is not sufficient involution, reperfusion is suspected and retreatment should be considered. The second goal on CT is to detect growth of residual small AVMs and the rare development of new AVMs. In the case of a negative CT chest 1 year after embolization, repeat follow-up in the future is recommended after 3 years [25].

For patients with HHT with negative transthoracic contrast echocardiography 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 year to detect growth and subsequent indication for embolization.

Pulmonary AVM precautions are recommended in all HHT patients with pulmonary AVMs, regardless of treatment, and also all HHT patients with a right-to-left shunt on transthoracic echocardiography, even if there are no CT-detectable AVMs. 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 SBE guidelines of the American Heart Association [25, 69]. Secondly, in order 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-eliminating filter, if available. Finally, it is recommended that patients avoid SCUBA diving to prevent complications from decompression.

Pregnancy and Pulmonary Arteriovenous Malformations

Pregnancy is associated with an increased risk of hemorrhage from pulmonary AVM [58, 60], presumably secondary to the increased cardiac output and increased stroke volume [71]. To reduce this risk, screening for the presence of pulmonary AVMs in HHT patients is recommended prior to pregnancy, with preventative treatment [20]. When pulmonary AVMs are newly diagnosed during pregnancy, embolization is recommended during the second trimester to prevent complications. If pulmonary AVMs are present and not treated during pregnancy, the pregnancy should be considered high-risk. 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 of the fluoroscopy time. Taking these precautions will expose the fetus to a radiation dose of <50–200 mrad, which is below the maximal occupational radiation dose for a pregnant worker of 500 mrad [30].

Children with Hereditary Hemorrhagic Telangiectasia

Children with HHT should be screened for pulmonary AVMs as well [19, 25]. Twenty-three percent of asymptomatic children with a HHT diagnosis have pulmonary AVMs, of these 70 % with a significant feeding artery diameter of ≥3 mm [2]. Initial screening for pulmonary AVMs in the pediatric population can be done by upright and supine pulse oximetry, chest radiography and/or transthoracic echocardiography [3, 25]. 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 or who are hypoxemic. Treatment of asymptomatic children should be considered on a case by case basis [25]. Treatment by transcatheter embolotherapy in children is low-risk in experienced hands, with complication rates comparable to those in adults [23].

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 %) of patients with diffuse pulmonary 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.

The mean PaO_2 at presentation is 47 mmHg and 75 % of patients have polycythemia due to chronic hypoxemia. Diffuse pulmonary AVMs are associated with an increased mortality of 25 % during a mean follow-up of 8.5 years, only reported in patients with bilateral involvement [22]. 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 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. Most common locations for other VMs are the brain and liver. Though there is no international consensus on asymptomatic screening for brain AVMs, this is the current standard of care in HHT Centres of Excellence across North America, using MRI. Diagnostic testing for the liver VMs is generally only recommended in symptomatic patients, since preventative treatment is not recommended [25], or in cases where the documentation of liver VMs might help complete the clinical criteria, in a given patient, for diagnosis of HHT.

Clinical vignette 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 VMs with 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) [61]. Patients with PH secondary to liver VMs mostly present with an increased cardiac output, while patients with class 1 PAH usually have an elevated mean pulmonary artery pressure and increased pulmonary vascular resistance [24, 29].

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 %) [56]. Only 5–8 % of patients with liver VMs are symptomatic, based on cross-sectional studies [9, 62]. Liver VMs are more prevalent in HHT patients over 40 years of age [8] and women appear to be more frequently affected than men [10]. Liver VMs with severe shunting can eventually lead to high output cardiac failure (HOCF), typically in the sixth or seventh decades of life. Rarely, women can also present with HOCF from liver VMs during pregnancy [35, 47].

HOCF 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 [24].

Patients with PH secondary to liver VMs typically present with symptoms of HOCF: 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 [13]. Triphasic hepatic CT, MRI or mesenteric angiography are options for diagnostic confirmation of liver VMs and also provide more detailed information reading the type(s) of shunting present as well as other complications (biliary cystic dilatation, focal nodular hyperplasia, etc.) [25].

The suspicion of PH and HOCF is generally confirmed on transthoracic echocardiography, 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, markedly increased cardiac output, normal pulmonary

vascular resistance, normal transpulmonary gradient and elevated pulmonary capillary wedge pressure [31].

Routine management of HOCF due to liver VMs includes salt restriction, diuretics, beta-blockade and treatment of anemia and atrial fibrillation [11].

Bevacizumab can be considered in refractory cases, and/or liver transplantation. Though experience with this antibody against vascular endothelial growth factor (VEGF) is limited, results have suggested it may have a role in these refractory cases, and transplantation may be avoided. Interestingly bevacizumab has been shown to improve the cardiac output in patients with liver VM and high cardiac output, with a complete response in 22 % of patients and a partial response in 65 % of patients at 6 months 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 [21].

Liver transplantation is considered in refractory liver VM patients, for HOCF, portal hypertension or biliary necrosis. 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 % [42]. 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 higher risk as liver transplantation in these patients is associated with increased mortality [26].

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 refractory disease who are not considered candidates for liver transplantation [12, 42].

Pulmonary Arterial Hypertension

Familial PAH is a rare disorder, with an estimated prevalence of 15 per million [37] and rarely caused by HHT. Within HHT patients, the prevalence of pulmonary arterial hypertension is not known.

PAH also occurs in HHT patients, though rarely (approximately 1 % of HHT patients). Most affected to date have *ACVRL1* mutation [32, 36, 64]. PAH can be suspected based on symptoms: dyspnea, syncope, fatigue, 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 estimated right ventricular systolic pressure (>40 mmHg) is found on routine transthoracic echocardiography. 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.

Complications from PAH in patients with HHT can be precipitated by anemia, leading to right heart failure. Patients with HHT are at risk for hemorrhage, most commonly from epistaxis or from telangiectasis in the gastrointestinal tract. Severe hemorrhage can lead to hypovolemia or anemia. Hypovolemia leads to a 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 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. Pulmonary vasodilators, i.e. bosentan, an endothelin receptor antagonist, have been reported to have a beneficial effect in patients with HHT and pulmonary arterial hypertension [7, 15], 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 [14]. 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 disease affecting 1 in 5,000–10,000 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 telangiectasia (Fig. 12.3), recurrent epistaxis, visceral AVMs and a positive family history. These characteristics are the four diagnostic criteria for HHT (Table 12.1). The diagnosis of HHT is definite if patients meet ≥3 criteria. The diagnosis is possible if they meet 2 criteria and the diagnosis of HHT is unlikely if patients meet ≤1 criterion [59].

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 [1]. The average diagnostic delay, between ENT consultation for epistaxis, and HHT diagnosis, is approximately 15 years [40].

Mucocutaneous telangiectasia are typically present on the lips, oral cavity, nasal mucosa and skin on the face and hands. Mucocutaneous telangiectasia increase in number during life. By the age of 20 years, 55–60 % of patients have visible mucocutaneous telangiectasia. By the age of 40, 100 % of patients has mucocutaneous telangiectasia [5, 6]. Visceral AVMs can be present in the lungs, liver, brain, spine, or any other organ. 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 12.2.

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.

Ninety percent of patients have a mutation in the *Endoglin* (*ENG*) gene on chromosome 9 (HHT-1) [50], or a mutation in the *Activin-A type II like kinase 1* (*ACVRL-1*) gene on chromosome 12 (HHT-2) [38, 46]. Less common mutations for HHT are mutations in the *SMAD4* gene on chromosome 18 [27] occurring in 2 % of patients [28], and generally associated with an overlapping juvenile polyposis syndrome. Approximately 85 % of patients with HHT have a mutation in one of these three genes [55]. Two other genes are associated with HHT as well, though the specific loci are not yet identified, chromosome 5 [16] and chromosome 7 [5, 6].

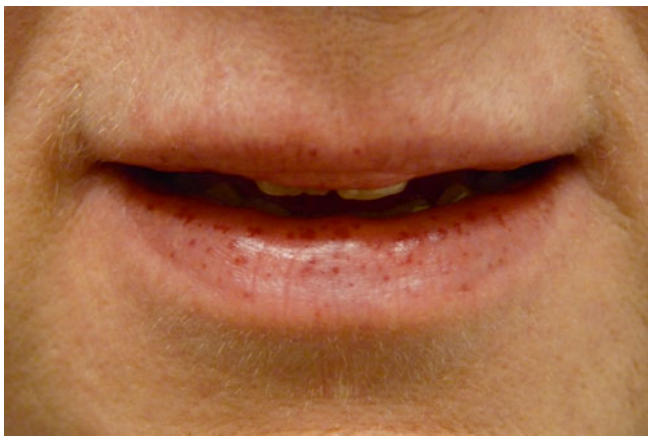

Fig. 12.3 Mucocutaneous telangiectasia on the lips

Table 12.1 Clinical diagnostic criteria for hereditary hemorrhagic telangiectasia

Mucocutaneous telangiectasia
Frequent recurrent spontaneous epistaxis
Visceral arteriovenous malformations
Affected first degree relative

Pathogenesis

Patients with a mutation in the *Endoglin* or *ACVRL1* gene have reduced levels of cell-surface Endoglin or ACVRL1 protein (haploinsufficiency model). Endoglin is a co-receptor for ligands of the transforming growth factor-ß (TGF-ß). ACVRL1 is a type I TGF-ß receptor. Both receptors are predominantly expressed on the surface of endothelial cells. Binding of TGF-ß to the AVCRL1-ALK5-TGFBR2 (TGF-ß type II receptor) receptor complex on the endothelial cell surface activates intracellular Smad1/5/8. Phosphorylation of Smad1/5/8 by Smad4 leads to transcription of pro-angiogenic target genes. Recruitment of Endoglin to the ACVRL1-ALK5-TGFBR2 receptor promotes the activation of Smad1/5/8 pathway. Mutations in Endoglin or ACVRL1 genes lead to an inefficiency of the Smad1/5/8 pathway and a defect in angiogenesis [34, 41].

ACVRL1 is involved in the bone morphogenetic protein (BMP-9) pathway as well. Binding of BMP-9 to the ACVRL1-BMPR2 (BMP type II receptor) receptor complex leads to activation of intracellular Smad1/5/8 [57]. Subsequent phosphorylation by Smad4 leads to inhibition of fibroblast growth factor, inhibition of VEGF-induced angiogenesis and stimulates vascular smooth muscle cell migration. Mutations in ACVRL1 affect this pathway as well [39, 68].

Table 12.2 Genotype-phenotype correlation of organ involvement in patients with hereditary hemorrhagic telangiectasia [43, 45, 56]

	Endoglin mutation (%)	*ACVRL1* mutation (%)
Pulmonary AVM	49–76	5–44
Cerebral AVM	9–22	0–4
Liver VM	8–60	41–83
Gastrointestinal telangiectasia	60–72	51–66

AVM arteriovenous malformation, *VM* vascular malformation

As such, *Endoglin* and *ACVRL1* mutations can lead to angiogenic dysregulation. The current thinking is that this angiogenic dysregulation characterizes an abnormal response to injury in HHT patients, leading to the development AVMs.

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Hepatopulmonary Syndrome

13

Karen L. Swanson

Introduction

Pulmonary vascular disease can occur in the setting of chronic liver disease. In one form, pulmonary vasoproliferation characterized by medial hypertrophy, intimal hyperplasia, and plexogenic pulmonary arteriopathy results in obstruction to pulmonary blood flow and "portopulmonary hypertension" [1]. In another form of pulmonary vascular disease associated with chronic liver disease, intrapulmonary vascular dilatations develop resulting in arterial hypoxemia with normal or low pulmonary vascular resistance leading to the "hepatopulmonary syndrome" (HPS) [1].

The diagnostic triad of chronic liver disease, arterial hypoxemia, and intrapulmonary vascular dilatations characterizes HPS (Box 13.1) [2]. The chronic liver disease generally involves cirrhotic or non-cirrhotic portal hypertension. Arterial hypoxemia is defined as an arterial PaO_2 of less than 70 mmHg or an alveolar-arterial oxygen gradient greater than 20 mmHg while breathing room air [1]. Some authors advocate using the age corrected alveolar-arterial oxygen gradient rather than a standard value of 20 mmHg. Intrapulmonary vascular dilatations are documented with either transthoracic contrast echocardiography or with brain imaging following lung perfusion scanning using technetium labeled macroaggregated albumin particles (^{99m}TcMAA).

Box 13.1
Diagnostic Criteria for Hepatopulmonary Syndrome

1. Presence of liver disease
   (a) Cirrhotic or non-cirrhotic portal hypertension
2. Intrapulmonary vascular dilatations
   (a) Positive transthoracic contrast/bubble echocardiogram
   (b) ^{99m}Technetium lung/brain perfusion scan
3. Hypoxemia
   (a) Seated room air PaO_2 <70 mmHg
   (b) Alveolar-arterial gradient on room air >20 mmHg

Prevalence rates for HPS in the literature have ranged from 5 to 29 % in patients with end-stage liver disease undergoing liver transplantation evaluation [2]. The true prevalence of HPS in patients with various stages of liver disease is unknown. In a large prospective study of 80 patients with cirrhosis undergoing liver transplant evaluation, the prevalence rate of HPS was 17.5 % [3].

Positive contrast echocardiography consistent with intrapulmonary shunt with *normal* gas exchange has been documented in patients with cirrhosis. Table 13.1 compares several studies of patients with cirrhosis evaluated using both contrast echocardiography and arterial oxygenation assessment. Positive contrast echocardiography documenting intrapulmonary vascular dilatation ranged from 3.0 to 20.0 % [3–6]. Arterial hypoxemia ranged from 0.0 to 17.5 %. It is conceivable that patients with positive contrast echocardiography consistent with intrapulmonary shunt, but normal gas exchange, have a higher incidence of developing HPS or have a "preclinical" form of HPS. These patients deserve prospective follow-up to determine their actual outcome.

HPS occurs with equal frequency in men and women and, also occurs in pediatric patients [7]. Portal hypertension appears to be a necessary component in the development of HPS [1]. The incidence of HPS is not related to any specific etiology of liver disease [1, 2, 6, 8]. Hypoxemia severity does not correlate with the severity of portal hypertension as measured by portal pressure or the severity of liver disease as measured by the Child-Pugh or MELD scores [6, 8]. Severity of hepatic dysfunction associated with portal hypertension does not predict the presence or severity of HPS. HPS has been documented in patients with mild degrees of hepatic dysfunction (Childs-Pugh "A") and hypoxemia has progressed in the setting of stable hepatic dysfunction.

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Table 13.1 The prevalence of positive transthoracic echocardiography in patients with portal hypertension in relation to abnormal oxygenation (true HPS)

	N	+ CE − hypoxemia	+ CE + hypoxemia	DLCO <80 %
Martinez et al. [3]	80	2 (3)	14 (17.5)	14 (18)
Mimidis et al. [4]	75	8 (10.7)	0	8 (11)
Gupta et al. [5]	54	4 (7.4)	6 (11.1)	5 (9)
Abrams et al. [6]	40	8 (20)	7 (17.5)	11 (14)

N total number, *CE* transthoracic contrast echocardiography; number (percent), *DLCO* diffusion capacity for carbon monoxide on pulmonary function testing

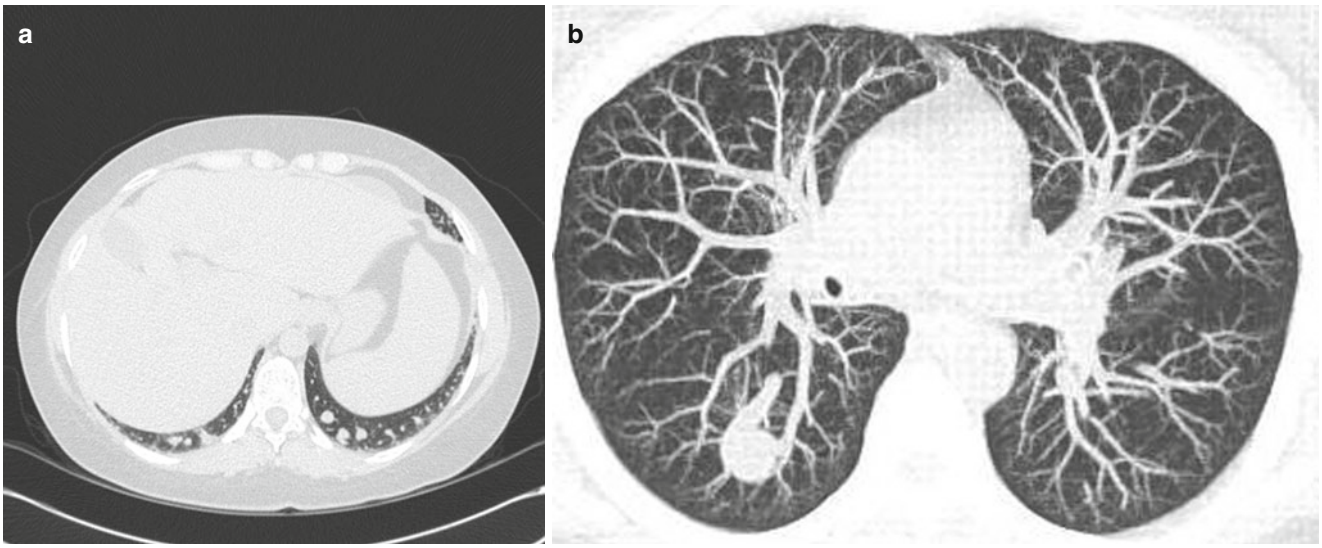

Fig. 13.1 (**a**) Type I dilatations consist of diffuse pre-capillary and capillary vascular dilatations between 15 and 500 μm in diameter. (**b**) Type II dilatations involve distinct arteriovenous communications

Pathophysiology

Gas exchange is the primary abnormality in HPS resulting in hypoxemia caused by pulmonary vascular dilations. A vascular imbalance between vasodilating and vasoconstricting mediators has been proposed as a probable cause for the pathologic changes seen at autopsy [2]. Normal capillary diameter in the pulmonary vascular system ranges from 8 to 10 μm [1]. Both autopsy studies and pulmonary angiography have demonstrated two different types of vascular dilatations in HPS; Types I and II (Fig. 13.1a, b). Remarkably, physiologic studies suggest that these changes can reverse following liver transplantation in most cases [9].

Type I dilatations consist of diffuse pre-capillary and capillary vascular dilatations between 15 and 500 μm in diameter [2, 10]. These types of dilatations lead to ventilation-perfusion mismatching caused by excessive perfusion for a given unit of normal ventilation. Type II dilatations involve distinct arteriovenous communications resulting in the *absence* of ventilation with increased perfusion and the presence of true anatomic shunting. The response to 100 % oxygen varies with both the degree and type of intrapulmonary vascular dilatations present [8]. With type I lesions, the response to 100 % oxygen may be near normal, while in a pure shunt (type II lesions), there will be minimal or no response to 100 % oxygen. Dilated pleural vessels similar to spider angiomata in liver disease can also be found in HPS, but they do not appear to participate in gas exchange [10].

The mechanism of hypoxemia in HPS is likely multifactorial and, in a given patient, may include the co-existence of other non-vascular reasons for hypoxemia [3, 8]. Patients with advanced liver disease often have pre-existing gas exchange abnormalities due to the presence of pleural effusions ("hepatic hydrothorax"), ascites, interstitial lung diseases, and/or obstructive lung disease (emphysema, bronchitis, or asthma). In the absence of these co-existing, "intrinsic" pulmonary abnormalities, at least three mechanisms of hypoxemia documented by the multiple inert gas elimination technique exist in HPS and are described in Table 13.2 [1, 2, 10]. First, due to the hyperdynamic circulation associated with advanced liver dis-

Table 13.2 Mechanisms of hypoxemia in hepatopulmonary syndrome are shown

Abnormality	Mechanism
1. *Hyperdynamic circulation*	Ventilation-perfusion mismatch
↑ Cardiac output = ↓ transit time in	Normal V/↑ Q
Capillary bed ↓ time for gas exchange (oxygenation)	
2. *Diffusion – perfusion limitation*	Ventilation-perfusion mismatch
(Type I intrapulmonary vascular dilatations)	Normal V/↑ Q
(a) ↑ distance to center of capillary = limitation to diffusion	Diffusion abnormality
3. *True right to left shunt*	Ventilation-perfusion mismatch
(Type II intrapulmonary vascular dilatations)	Shunt = absent V/↑ Q
4. *Intrinsic cardiopulmonary disease if present*	

Any combination of the four abnormalities may be present in patients with HPS resulting in both varying severities of hypoxemia and responses to oxygen therapy

V ventilation, *Q* perfusion

ease, the increased cardiac output decreases the transit time through the pulmonary circulation decreasing the time for capillary oxygenation resulting in ventilation-perfusion mismatching (normal ventilation with excessive perfusion).

A second mechanism of hypoxemia relates to a diffusion-perfusion limitation due to the presence of Type I diffuse intrapulmonary vascular dilatations. As the degree of dilatation increases, distance from the alveoli to the center of the capillary increases and passive diffusion of oxygen molecules is limited. With a higher partial pressure of alveolar oxygen (obtained while breathing 100 % oxygen), there is an increased driving force for oxygen to diffuse into the capillaries, resulting in a dramatic increase in PaO_2 despite severe hypoxemia breathing room air [8]. Such diffusion limitation in combination with the possible increased blood transit time from the hyperdynamic circulation seen in liver disease can result in severe arterial hypoxemia at rest (PaO_2 <50 mmHg).

The third mechanism of hypoxemia is the presence of right to left anatomic intrapulmonary shunting. This is uncommon as demonstrated by pulmonary angiography or contrast enhanced CT scanning of the chest. Unoxygenated venous blood simply bypasses gas exchange units via direct arteriovenous communications of varying size and configuration. If large (>5 mm in diameter), they may be amenable to coil embolotherapy. These abnormalities may result in severe hypoxemia with very poor response to 100 % inspired oxygen (PaO_2 <300 mmHg) [8].

The interaction of vascular mediators between the liver and the lung has been a subject of much interest. Is the diseased liver tilting the balance between vasodilating and vasoconstricting substances so that there is an unopposed action of vasodilators? Does the pulmonary vascular bed require vasomodulating factors produced by the liver to maintain control of the pulmonary circulation? An intriguing response to this question may be found in the pediatric congenital heart disease literature. Pulmonary vascular dilatation with severe hypoxemia develops *after* the creation of cavopulmonary shunts as a treatment approach to tricuspid atresia (and its associated vascular abnormalities) [11]. In patients who had aberrant hepatic venous drainage (emptying into the left atrium), arterial hypoxemia and intrapulmonary vascular dilatations resolved with redirection of the hepatic venous effluent into the pulmonary arterial circulation. This well-documented experience provides evidence for a probable vascular mediator arising from the liver that affects the structure and vasomotor tone of the pulmonary circulation.

In a bile duct ligation rat model of HPS, pulmonary vascular endothelial nitric oxide synthase levels are increased resulting in a rise in nitric oxide that correlates with the development of pulmonary vasodilatation [12]. Nitric oxide is a potent vasodilator. In a subsequent study by the same investigators, both hepatic and plasma endothelin-1 levels were increased after bile duct ligation in the rat with subsequent portal hypertension [13]. Endothelin-1 is a potent vasoconstrictor. In this situation, endothelin-1 likely acts on the endothelin-B receptors on the endothelial cell to stimulate nitric oxide production and endothelin-1 clearance. The plasma endothelin-1 levels positively correlated with pulmonary endothelial nitric oxide synthase levels and with alveolar-arterial oxygen gradients. No human studies have addressed the endothelin-B hypothesis to date. Indeed, increased levels of exhaled nitric oxide have been documented in HPS at levels (ppb) greater than those measured in cirrhotic patients without hypoxemia [2, 10].

One non-invasive form of evaluating airway mediators includes the measurement of breath markers. Exhaled nitric oxide levels are increased in HPS patients and decline after liver transplantation [14–17]. Extended nitric oxide analysis rather than single breath exhalation flow rates may be helpful in differentiating the actual production site of NO within the respiratory system i.e. alveolar versus airway production of NO [18].

Tumor necrosis factor alpha (TNFα) levels are increased in the common bile-duct ligation rat model of HPS presumably from bacterial translocation resulting in endotoxemia stimulating production of TNFα [19–22]. TNFα further increases NO levels. Pentoxifylline has been shown to improve HPS by blocking TNFα however additional adverse reactions limited its further evaluation [22, 23]. More recently, Liu and colleagues have shown that a specific monoclonal antibody to TNFα improves HPS in cirrhotic rats mediated through the inhibition of TNFα PI13/Akt-NO pathway [24]. Figure 13.2 illustrates the delicate interaction of the various mediators between the liver and the lung.

In addition to the research on various mediators involved in HPS, genetic risk factors for HPS in patients with advanced liver disease have also been assessed. In a multicenter case-control study of patients with cirrhosis being evaluated for liver transplant, 59 cases of HPS were compared with 126 control patients without HPS [25]. Forty-two single nucleotide polymorphisms in 21 genes were significantly associated with HPS after adjustments for race and smoking. The authors concluded that common genetic variation influences the pathogenesis of HPS and that future studies focusing on genetic patterns are necessary.

Clinical Vignette

A 14 year old female was referred to pulmonary clinic complaining of progressive dyspnea on exertion over the last 12 months; WHO class III functional status. She had developed fatigue and was only able to participate in the first and last periods of school classes per day due to profound dyspnea. Upon presentation, room air arterial blood gas showed the partial pressure of oxygen to be 46 mmHg with an oxygen saturation of 82 %. Pulmonary function studies were normal with the exception of a reduction in diffusion capacity.

On physical examination, cyanosis and clubbing were present. The lung examination was normal and the cardiac examination showed a hyperdynamic state with a grade two systolic murmur present. Mild splenomegaly was identified and there were no hepatic or abdominal bruits.

Computed tomographic chest scan with contrast showed mild cardiomegaly and a prominent spleen with normal lung parenchyma and no evidence of pulmonary embolus. Transthoracic bubble echocardiogram documented a large right to left intrapulmonary shunt. There

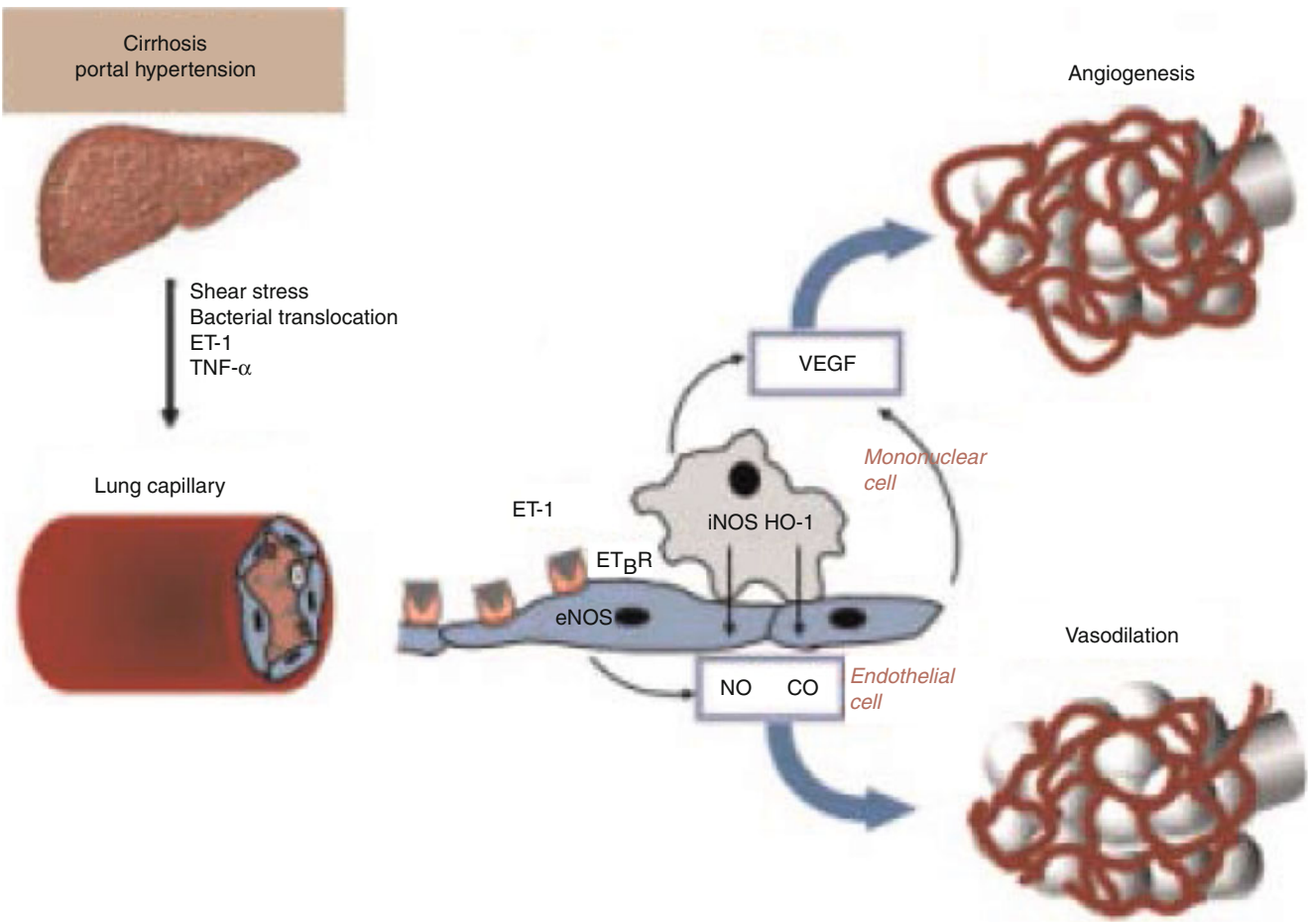

Fig. 13.2 Pathophysiology of hepatopulmonary syndrome. *ET-1* endothelin 1, *TNFα* tumor necrosis factor α, ET_BR endothelin B receptor, *eNOS* endothelial nitric oxide synthase, *iNOS* inducible nitric oxide synthase (With permission from Machicao and Fallon [50], Thieme Publishers)

was no evidence of pulmonary hypertension or valvular heart disease. Nuclear medicine lung-brain perfusion scanning showed a shunt fraction of 66 %. Right and left heart catheterization was performed. Mean pulmonary artery pressure was 31 mmHg with a pulmonary capillary wedge pressure of 17 mmHg and a cardiac output by thermodilution of 9.48 l/min (confirmed by Fick technique). Transjugular liver biopsy was unsuccessful due to chronic stenosis and occlusion involving the hepatic vein confirmed by MR angiography.

Percutaneous liver biopsy was essentially unrevealing. Alkaline phosphatase was 191; AST 82; ALT 58; bilirubin 1.5; GGT 78; ammonia 39; and ferritin 372. Contrast computed tomographic abdominal scan revealed evidence of portal hypertension with a nodular contour to the liver compatible with mild sclerosis; an unusual perfusion pattern; numerous mesenteric varices including paraduodenal veins, varices within Morrison's pouch, peripancreatic and portal systemic collaterals anteriorly within the abdomen; and a recanalized umbilical vein.

The clinical diagnosis of HPS was established based on the findings of portal hypertension, arterial hypoxemia, and intrapulmonary shunting. She also had an elevation in mean pulmonary artery pressure and pulmonary capillary wedge pressure with high cardiac output resulting in a hyperdynamic state with post-capillary pulmonary hypertension. She underwent an orthotopic liver transplant. Pathology of the patient's diseased liver showed nodular regenerative hyperplasia with focal septal fibrosis. The patient was discharged on 10 l oxygen after 26 days. Nine months later, the patient was off supplemental oxygen with a normal overnight oximetry; oxygen saturation on room air of 95 %; and lung-brain perfusion shunt fraction of 12 %. Cardiopulmonary hemodynamics normalized.

Clinical Features

The clinical features in HPS are those typically seen in underlying liver disease. On physical examination these include spider angiomata, palmar erythema, gynecomastia, splenomegaly, and jaundice. As the severity of HPS increases, other physical findings may evolve, including cyanosis, tachypnea, clubbing, and orthodeoxia. Orthodeoxia is defined as a decrease in arterial PO_2 greater than 3 mmHg in the upright versus the supine position [10, 26]. Patients frequently present with the insidious onset of dyspnea and platypnea (dyspnea exaggerated in the upright position). Orthodeoxia and platypnea although uncommon, are two of the cardinal manifestations of HPS although are not specific for HPS. Worsening hypoxemia in the upright position is due to the increased presence of intrapulmonary vascular dilatations in the mid and basilar portions of the lungs. In the upright position, there is increased perfusion to these dependent areas with worsening ventilation-perfusion mismatching and hypoxemia. When compared to patients with cirrhosis alone, HPS patients have higher incidences of finger clubbing, spider angiomas, and dyspnea [2]. Progressive hypoxemia may occur in the setting of apparently stable hepatic dysfunction [27].

Diagnosis

The diagnosis of HPS is made in the setting of arterial hypoxemia with intrapulmonary vascular dilatation in the setting of chronic liver disease [1]. The hypoxemia in HPS is defined as an arterial PO_2 of less than 70 mmHg or an alveolar-arterial oxygen gradient of greater than 20 mmHg (some authors use 15 mmHg) [1, 2]. Arterial blood gases obtained in both the supine and upright position will document the presence and severity of orthodeoxia. Similarly arterial blood gases on room air and 100 % oxygen will document the presence or absence of a true shunt by the response to oxygen. The shunt fraction can be estimated by the 100 % oxygen technique however is based on several assumptions and, in the hyperdynamic state generally present in chronic liver disease, can result in the shunt equation underestimating the true shunt [28].

Two-dimensional transthoracic contrast echocardiography is the most sensitive test to detect the presence of right to left shunting [6]. It is not able to differentiate between the two different types of intrapulmonary vascular dilatations, however can differentiate between intrapulmonary and intracardiac sources of right to left shunt. Contrast echocardiography detects vascular dilatation via micro-bubbles (diameter 10–60 μm) created by hand-agitated saline injected into a peripheral arm vein. Normally these micro-bubbles are absorbed at the capillary-alveolar level through the first pass into the pulmonary circulation. If vascular dilatations exist, the micro-bubbles pass through the pulmonary vascular bed into the left atrium where they can be seen three to five cardiac cycles after the appearance in the right ventricle. If micro-bubbles are seen in the left heart within three cardiac cycles, then an intracardiac shunt may exist (atrial or ventricular septal defect). Helpful indirect echocardiographic markers of HPS compared to non-HPS cirrhotic patients also include left ventricular enlargement and higher systolic velocity in the mitral valve [29].

The degree of intrapulmonary vascular dilatation can be quantified both by transthoracic contrast echocardiography and by lung-brain perfusion scanning with technetium-99 labeled macroaggregated albumin (^{99m}TcMAA) [8, 30]. Quantification of right to left shunt by contrast echocardiography is performed by grading the degree of bubble opacification of the left ventricle after the administration of the

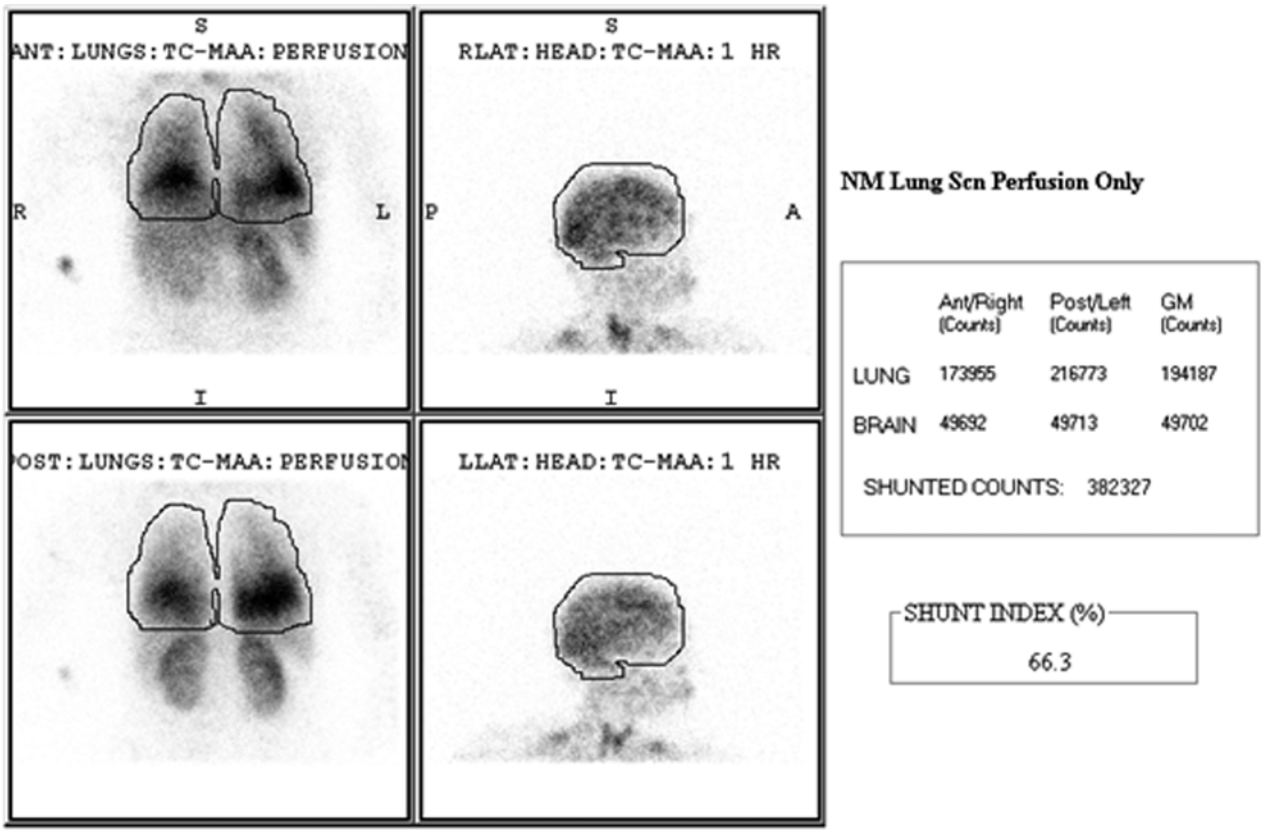

Fig. 13.3 Lung perfusion scanning with brain imaging using technetium-99 labeled macroaggregated albumin (assumes 13 % cardiac output to brain)

microbubbles through a peripheral vein [31–34]. This may be helpful in determining which patients go on to computed tomography scanning of the chest looking for distinct AVMs and has been shown to be helpful in Hereditary Hemorrhagic Telangiectasia as well as congenital PAVM. It should be remembered that although the vascular dilatations may include true anatomic shunts, the ^{99m}TcMAA method (or contrast echocardiogram) does not distinguish between types of vasodilatation. Figure 13.3 shows a positive lung-brain perfusion scan with the intrapulmonary right to left shunt quantified at 66 %. Normal shunt fractions are less than 6 %. This radionuclide scan is specific for the diagnosis of HPS in the setting of chronic liver disease and hypoxemia if the shunt fraction is greater than or equal to 6 % [30].

The lung/brain perfusion scan quantitates the oxygenation abnormality in HPS, since it is specific for vascular dilatation and not affected by other nonvascular reasons for hypoxemia [8, 30]. The technetium labeled macroaggregated albumin, with diameters between 20 and 90 μm, passes through the dilated pulmonary vascular bed and can be detected by imaging over the brain and kidneys. Abrams et al. studied the role of macroaggregated albumin lung/brain perfusion scans in the diagnosis of HPS given that many cirrhotics have positive contrast echocardiography in the absence of hypoxemia [30]. They found that the lung/brain perfusion scans were positive in 21 of 25 patients with HPS (84 % sensitivity) and *negative in all controls* (cirrhotic patients with normal contrast echocardiograms). All patients with positive lung/brain perfusion scans were hypoxemic with PO_2 values <60 mmHg. They concluded that a positive lung/brain perfusion scan in cirrhosis was specific for the presence of HPS. They also found a strong inverse correlation between the quantitated shunt fraction and room air arterial PO_2 and, a strong direct correlation between the shunt fraction and the alveolar-arterial oxygen gradient.

Lung-brain perfusion scanning is not without fault. Kalambokis and Tsianos in a letter to the editor of 'Liver International' outline three potential drawbacks of the test as a diagnostic tool for HPS [35]. First, there is a major operator-dependent aspect in identifying areas with abnormal radioactive tracer uptake that may produce differences in the reading of the test with discrepant results. For example, positive results (shunt fraction >6 %) have been reported in 0–20 % of patients with cirrhosis but normal oxygen levels [4, 36]; and, in 20–96 % of cirrhotic patients with positive contrast echocardiogram [6, 8, 30]. Second,

the shunt fraction "normal" cut off of 6 % was adopted based on the findings of one study showing a shunt fraction of 3.5 ± 1.27 % in 10 healthy subjects [6]. Third, the shunt fraction measurement is based on calculations using an estimated 13 % of the cardiac output to the brain. A decrease in intracranial blood flow exists in patients with cirrhosis and this seems to increase as severity of liver disease increases [37]. Thus cerebral vasoconstriction could result in underestimation of the shunt fraction in advanced cirrhosis.

In patients with a large shunt by ^{99m}TcMAA lung/brain perfusion scanning and a poor response to 100 % oxygen (PaO_2 <300 mmHg; normal >500 mmHg), pulmonary angiography may be indicated to determine if discrete arteriovenous communications are present. These vascular lesions are often amendable to vascular intervention with coil embolotherapy and elimination of shunting. More frequently in HPS however, the intrapulmonary vascular dilatations are small and diffuse with normal pulmonary angiograms when performed. Computed tomography scanning of the chest may be helpful in determining other etiologies for hypoxemia and may rarely show a distinct pulmonary arteriovenous malformation. One potential algorithm for evaluating patients with suspected HPS can be seen in Fig. 13.4.

Finally, a reduction in the single breath diffusing capacity for carbon monoxide (DLCO) is the most common abnormality observed on pulmonary function tests in patients with any type of chronic liver disease; it is not specific for HPS [2, 10]. An abnormal diffusing capacity may correlate quite closely with the severity of hypoxemia due to HPS, at least prior to liver transplantation. There are no patterns in expiratory flow or the flow-volume loop that are specific for HPS. Similarly, no specific findings on chest roentgenogram exist for the diagnosis of HPS. Chest radiographs can show basal shadowing, specific arteriovenous malformations (uncommon), pleural effusions, or may be normal. On conventional computed tomography scanning of the chest, peripheral pulmonary vascular dilatations can be seen with normal central pulmonary artery diameter but most commonly are normal [38].

Management

The treatment of HPS can be focused on three areas as seen in Table 13.3. The first intervention involves supplemental oxygen to treat hypoxemia. Some patients will respond quite well simply to the administration of oxygen. However, as the severity of the intrapulmonary vascular dilatations progresses, oxygen alone will be less effective. A second focus of therapy is in the treatment of the pulmonary vascular dilatations. Presently, there is no consistently effective treatment for the Type I dilatations. Several agents discussed below have been used with various degrees of success. Treatment for the Type II dilatations causing right to left shunting involves coil embolotherapy. The Type I dilatations are more commonly seen however. Treatment of the underlying liver disease is the third aim of treatment, although HPS can progress even with stable hepatic dysfunction.

Rarely, HPS spontaneously resolves [10, 28]. Pharmacologic treatment in the management of HPS has been disappointing thus far. Many agents have been tried without much benefit including almitrine, antimicrobial agents, prednisone, indomethacin, and octreotide [10, 28]. Methylene blue administered intravenously to seven patients with moderate to severe HPS was found to improve oxygenation with a maximum effect seen at 5 h and continued improvement at 10 h following a single infusion [39]. This supports the idea of nitric oxide induced pulmonary vasodilatation. Allium sativum (garlic) has also been shown to improve oxygenation in 6 of 15 patients with HPS in a prospective, pilot study to determine if a standardized garlic powder improved oxygenation and dyspnea in HPS [40]. Interventional radiology techniques including transjugular intrahepatic portosystemic shunting (TIPS) and cavoplasty (for portal hypertension caused by inferior vena cava obstruction due to chronic Budd-Chiari syndrome) are additional interventions with variable results in HPS [41, 42].

There is no question that HPS can resolve following liver transplantation (LT) [9, 27]. Recurrence of HPS after LT is rare. Many institutions currently consider HPS to be an indication for LT even in the setting of stable hepatic dysfunction as long as transplant-listing criteria are met [2, 27]. In a review of 81 total patients undergoing LT as treatment for HPS, Krowka et al. found an overall mortality of 16 % within 3 months after LT [27]. No intraoperative deaths occurred. In this literature review, 82 % of patients undergoing LT for HPS experienced an improvement in or normalization of hypoxemia within 15 months following LT. Unfortunately, case reports have described the resolution of HPS following LT with the subsequent development of pulmonary hypertension [43]. This is an uncommon occurrence and patients who may develop this phenomenon cannot be identified before transplant. Genetic abnormalities that may affect vascular mediators and the development of pulmonary hypertension are under study. Several case reports and case series are emerging showing that living donor LT successfully reverses the hypoxemia of HPS as well [44–46].

An important area of interest is the optimal timing of when LT should be performed in patients with HPS. The United Network for Organ Sharing (UNOS) is a nonprofit charitable organization that maintains the organ transplant waiting list in the United States. The UNOS policy regarding

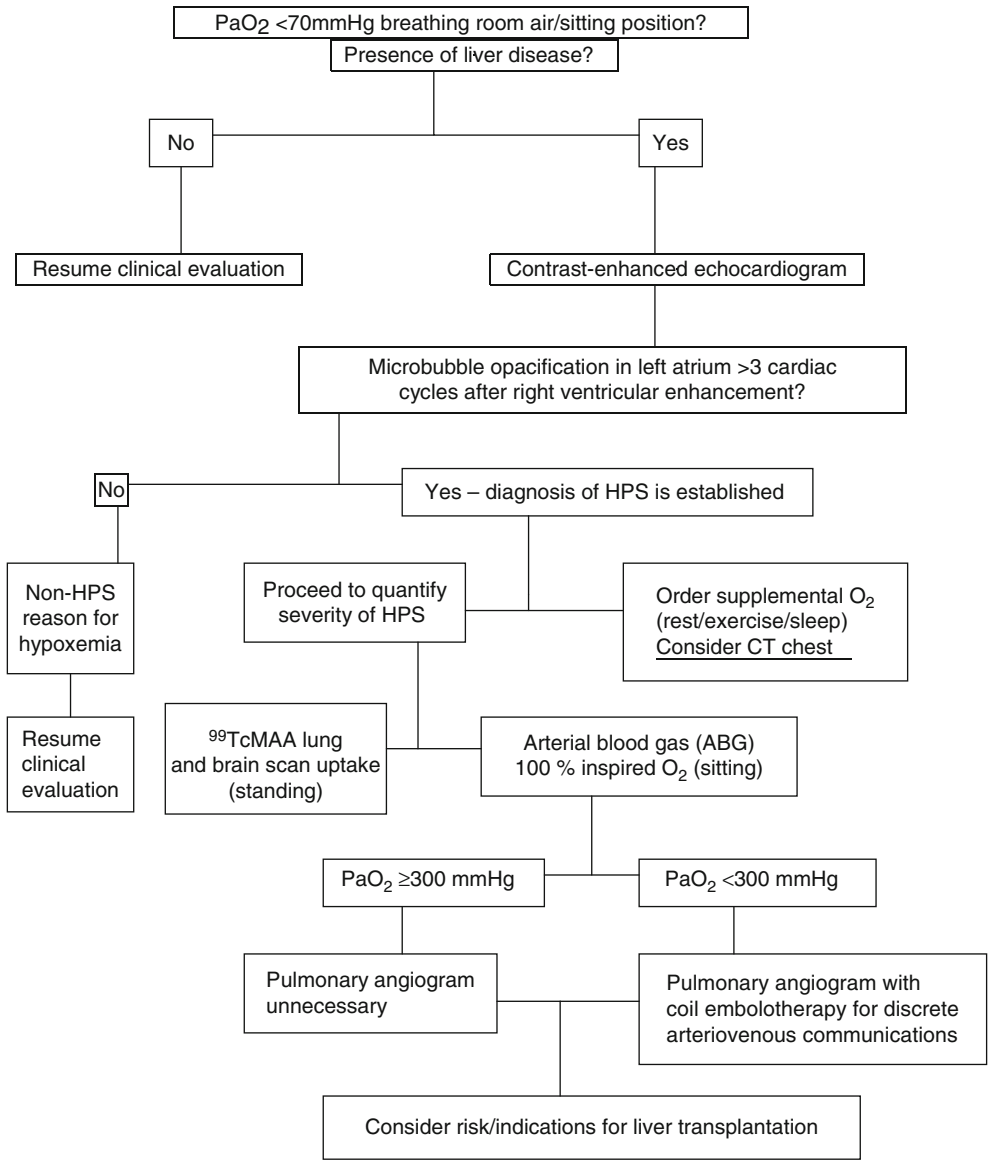

Fig. 13.4 Diagnostic algorithm for hepatopulmonary syndrome screening and diagnosis

Table 13.3 Hepatopulmonary syndrome treatment options

	Pharmacology	Interventional	Surgery
Hypoxemia	Oxygen		
Pulmonary vascular dilatation	Multiple agents attempted (see text)	Coil Embolotherapy (Type II)	
Hepatic dysfunction		Transjugular intrahepatic portosystemic shunt (TIPS)	Liver transplant
		Cavoplasty	

LT adopted the Model for End-Stage Liver Disease (MELD) scale to assess a patient's risk of 3-month mortality on the waiting list so that patients could be better prioritized based on the severity of their illness, using objective, verifiable medical criteria. The MELD scale is a continuous disease severity scale (based upon levels of bilirubin, creatinine, and INR) that is highly predictive of the risk of dying from liver disease for patients waiting on the transplant list [47].

Patients with HPS may have stable hepatic dysfunction so that their MELD score may not reflect their need for urgent LT. Because of this, UNOS and the Liver Disease Severity Scale Committee developed guidelines for adjusting the

MELD score for this group of patients. The current policy now states that "patients with clinical evidence of portal hypertension, evidence of a shunt, and a PaO_2 <60 mmHg on room air may be referred to the Regional Review Board for consideration of a MELD score that would provide them a reasonable probability of being transplanted with 3 months".

Prognosis

The natural history of HPS is slowly being defined. Most patients with HPS will continue to deteriorate with worsening hypoxemia and dyspnea despite stable hepatic dysfunction unless transplanted. Nonetheless, some prognostic factors have been defined by reviewing the literature. In the review by Krowka et al. [27], transplanted patients who died had significantly lower mean PO_2 values compared with patients who survived (44.7 mmHg vs 54.2 mmHg; $P<0.03$). Also 30 % of patients with severe hypoxemia, defined as a PO_2 <50 mmHg, died after LT compared with those with a PO_2 >50 mmHg ($P<0.02$). A case-control study by Mayo Clinic comparing 61 HPS patients with 77 patients without HPS matched for liver disease cause, MELD, and age showed that without transplantation, HPS patients had worse 5-year survival than matched controls ($p=0.0003$) [48]. HPS patients also showed a decline in PaO_2 of about 5 mmHg per year; and, HPS patients not undergoing transplant had a median survival of 24 months. Five year survival from the time of LT in HPS patients with severe hypoxemia was similar to that of controls (55 % vs 84 %; $p=.67$). Only by gaining an understanding of the natural history and prognostic factors involved in HPS, will investigators be able to determine the optimal timing of LT in these patients.

Following LT, many patients with HPS will develop worsening hypoxemia in the post-operative period. Resolution of hypoxemia may take weeks to months in which the patient needs to be supported with supplemental oxygen as seen in the clinical vignette. Chihara and colleagues describe their experience in five patients using non-invasive ventilation in the immediate post-transplant period after extubation if the pre-operative PO_2 <60 mmHg [49]. They found that none of the patients required re-intubation and, that there were no problems with hypotension, pneumothorax, or aspiration pneumonia. Duration of non-invasive ventilation ranged from 11 to 88 days and that 4/5 patients were on room air at the time of discharge.

Summary

HPS is an uncommon condition generally resulting in progressive hypoxemia caused by increasing intrapulmonary vascular dilatations in patients with chronic liver disease. The degree of hypoxemia caused by HPS does not appear to be related to the severity of the liver disease. Many patients with end-stage liver disease may complain of dyspnea, however a high degree of suspicion in patients with liver disease and hypoxemia will enable clinicians to suspect HPS. The evaluation of these patients is focused on the documentation and severity of hypoxemia and intrapulmonary vascular dilatations with arterial blood gases, contrast echocardiography, and lung perfusion-brain scanning. Treatment of the underlying liver disease and alleviating hypoxemia with the use of oxygen is appropriate. LT currently is the mainstay of therapy for the treatment of HPS. As further insight emerges regarding the vascular mediators involved, future drug therapy may involve manipulation of these various mediators.

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Non-langerhans Cell Histiocytosis- Including Erdheim-Chester Disease- and the Lung

14

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Introduction

The etiologies of the accumulation of histiocytes within the lung are various as shown in Table 14.1: reactive conditions, infectious causes; storage diseases, primary histiocytic disorders discussed further more in detail in this chapter, and malignant histiocytic neoplasms. These entities often constitute a problem of differential diagnosis. For example, to illustrate these diagnostic difficulties, the foamy macrophages – a hallmark sign of Erdheim-Chester disease – can also be seen in non-specific conditions such as interstitial pneumonitis as well as storage diseases such as Niemann-Pick as discussed further in this chapter. Therefore, we will see that it is of the utmost importance to take into account the clinical and biological data, imaging features, and if necessary pathological findings, to make a diagnosis of non Langerhans cells histiocytosis in the lung.

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Erdheim-Chester Disease (ECD)

A Increasingly Well Recognized Multisystemic Disease: A General Review (Apart from the Lung)

Historical Considerations

Erdheim-Chester disease (ECD) is a rare, non-Langerhans form of histiocytosis of unknown origin. It was first described as "lipoid granulomatose" by Jakob Erdheim's student William Chester, in 1930 [1]. More than 500 distinct cases have since been reported [2]. ECD is characterized by the xanthomatous or xanthogranulomatous infiltration of tissues by foamy histiocytes, "lipid-laden" macrophages or histiocytes, surrounded by fibrosis [3, 4]. It can be distinguished from Langerhans cell histiocytosis (LCH) on the basis of the immunohistologic characteristics of histiocytes, as the cells stain positive for CD68 and negative for CD1a in ECD. In most cases (80 %), staining for the S-100 protein is also negative.

Two signs highly evocative of ECD are the nearly constant tracer uptake by the long bones on ^{99}Technetium bone scintigraphy and a "hairy kidney" appearance on abdominal CT scan present in approximatively 50 % of cases. Diagnostic criteria classically used are mentioned in the "box criteria".

Demographic Characteristics

Based on our experience with 75 patients, published in 2012, there is a strong male predominance in this disease, with 73 % of patients being male and only 27 % female [5]. Mean age at diagnosis in the two large series published was relatively stable: 55 years ±14 (range, 16–80 years) in the 2011 series [2]. ECD is far less frequent in children, as only eight pediatric cases have been reported, all with no cardiac involvement [6, 7].

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Table 14.1 Histiocytic disorders of the lung: morphological features and immunophenotype

Histiocytic disorder	Morphology	Immunophenotype
Reactive histiocytic conditions		
Non-specific interstitial pneumonitis	Polymorphous infiltrate containing macrophages	
Bronchiolar obstruction	Foamy cells	
Healing process		
Infections		
Mycobacteria infections	Foamy histiocytes PAS+/Ziehl+	
Whipple disease	Foamy histiocytes PAS+/Gram+	Antibody to T whipplei
Malakoplakia	Michaelis-Gutmann bodies PAS+/Perls+/Von Kossa+	
Crystal-storing histiocytosis	Immunoglobulin crystals within macrophages	CD68+ Light-chain restriction in macrophages and plasma cells
Storage diseases		
Gaucher's disease	PAS+, wrinkled paper aspect	CD68+
Niemann-Pick's disease	Foamy cells	CD68+
Primary histiocytic disorders		
Langerhans cell histiocytosis (LCH)	Folded nucleus, pale cytoplasm Eosinophils	CD1a+/CD207+/S100+/CD68±BRAF(V600E) ±
Erdheim-Chester disease (ECD)	Round or oval nucleus Pale or foamy cytoplasm Multinucleate giant Touton cells Lymphocytes, plasma cells	CD1a–/CD207–/S100±/CD68+/FXIIIa+BRAF(V600E) ±
Rosai-Dorfman disease (RDD)	Round or oval nucleus Pale or foamy cytoplasm Multinucleate giant cells Emperipolesis Lymphocytes, many plasma cells	CD1a–/CD207–/S100+/CD68+/FXIIIa–
Histiocytic malignant neoplasms		
Histiocytic sarcoma	Pleomorphism Atypical nucleus Mitoses	CD68+/CD163+CD1a–/CD21–/CD35–Myeloperoxidase–
Follicular dendritic cell sarcoma	Spindle shaped tumor cells Ovoid or elongated nuclei Storiform pattern	CD23+/CD21+/CD35+
Interdigitating dendritic cell sarcoma	Spindle shaped tumor cells Ovoid or folded nuclei	S100+/CD68–/CD163–CD1a–/CD21–/CD35–
Primary Langerhans cell sarcoma	Pleomorphism Atypical nucleus Mitoses	CD1a+/CD207+/S100+

Clinical Phenotypes

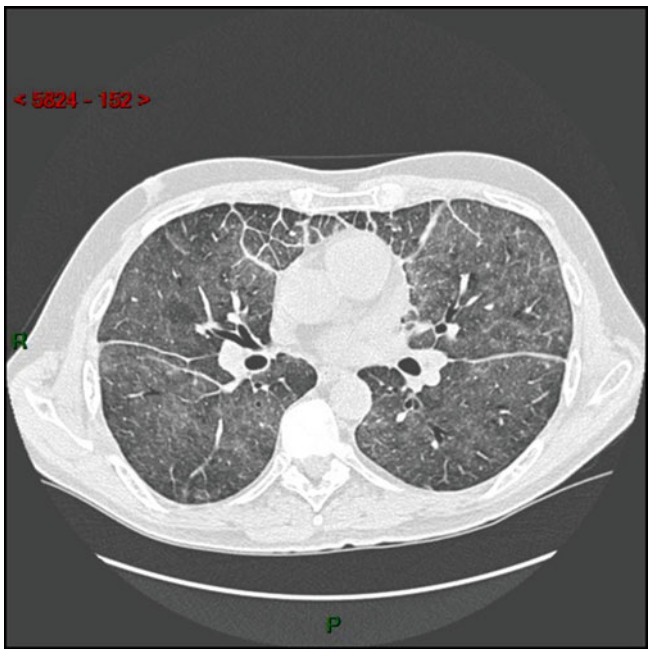
ECD is a truly systemic disease, with diverse signs, including skeletal involvement with bone pain, exophthalmos, diabetes insipidus, xanthelasma, interstitial lung disease, bilateral adrenal enlargement, retroperitoneal fibrosis with perirenal and/or ureteral obstruction, renal impairment, testis infiltration, central nervous system (CNS) and/or cardiovascular involvement [2, 4]. The frequency of the main clinical and radiological characteristics in ECD are presented in Table 14.2. The baseline clinical evaluation recommendations for patients diagnosed with ECD are also listed in a box.

The clinical course of ECD depends largely on the severity and distribution of the disease, and may range from asymptomatic bone lesions to multisystemic, life-threatening forms with a poor prognosis.

Clinical Vignette

The patient was a 55 year-old man who was diagnosed with pituitary adenoma in 2012 after a 5 year-history of diabetes insipidus. At that time, he was admitted in Intensive Care Unit for respiratory failure, which was attributed to an infectious disease. In March 2013, he presented with a second episode of respiratory failure and chest physicians were puzzled by an unusual septa

infiltration on chest CT scan (see Clinical Vignette figure). Systemic explorations revealed bilateral symmetric femoral and tibial bones, lung and suprasellar involvement, with no cardiac or retroperitoneal infiltration. Diagnosis of ECD was finally made from the xanthelasma biopsy which demonstrated foamy CD68+ CD1a– histiocytes, in which $BRAF^{V600E}$ mutation was found.



HRCT scan of the lung: axial image showing diffuse ground glass opacities, thickening of interlobular septa in the anterior parts of the lungs and thickening of the fissures due to a thickening of the subpleural interstitium.

Table 14.2 Frequency of the main clinical and radiological characteristics in Erdheim-Chester disease

	From the literature, %	Personal experience, %[a]
Bone pain	50	40[b]
Peri-aortic infiltration	60	66
"coated aorta" (sheathing of the whole thoraco-abdominal aorta)	30	23[b]
Pericardial involvement	45	42
Exophthalmos	27	25
Diabetes insipidus	27	25[b]
Xanthelasmas	19	28
"hairy kidney" aspect	ND	68
CNS involvement	15–25	51
Pulmonary involvement	22	43
Death	60	26

Taken from Ref. [5]
ND no data available
[a]In all cases, unless mention of comparison with another series, based on the 53 patients series published in 2011 [2]
[b]Compared to the 48 patients followed at Pitié-Salpêtrière Hospital (Taken from the 53 patients from the series published in 2011 [2])

Treatments

Until 2005, treatments for ECD included steroids, cytotoxic agents [8] and double autologous hematopoietic stem-cell transplantation [9, 10]. The efficacy of these treatments was difficult to assess, because each individual treatment had been used in only a few patients or in combination with other drugs and follow-up periods were often short. Braiteh et al. treated three ECD patients with interferon alpha (IFNα) and reported a rapid, substantial and durable regression of retro-orbital infiltration and gradual improvements of bone lesions, pain and diabetes insipidus [11]. However, we found, in eight patients with ECD, that the efficacy of low-dose IFNα (3 MU × 3/week) differed between patients and with the disease sites involved [12]. Moreover, symptoms did not always respond to IFNα at such doses, particularly in patients with severe multisystemic forms of ECD (CNS and cardiovascular involvement) [2]. We therefore recommend the use, if possible, of higher doses, of up to 9 MU × 3/week, which may be more effective for the treatment of meningeal infiltrations, sub- and retrosellar masses, pericardial and pseudo-atrial infiltrations. Long-term treatment should be considered, although it may be difficult to achieve due to side effects, such as depression and fatigue. IFNα has given much less convincing results for the treatment of pseudodegenerative forms of ECD with cerebellar involvement (similar to those observed in LCH).

IFNα appears to be a valuable first-line therapy for the prolonged treatment of ECD. A recent survival analysis revealed that treatment with IFNα and/or PEGylated IFNα was a major independent predictor of survival in a series of 53 patients (HR = 0.32; 95 % CI, 0.14–0.70; $P = 0.006$) [2]. The current therapeutic approach involves the initiation of treatment with PEGylated forms of IFNα, which are often better tolerated in the long term.

In 2010, there were several reports suggesting that imatinib mesylate was an effective treatment for histiocytoses [13], although a preliminary experience, with six ECD patients, was disappointing [14]. In the same year, recombinant human interleukin-1 receptor (anakinra) was also reported as a promising treatment in two patients with ECD, but these patients had no cardiovascular or CNS involvement [15]. Given the efficacy of cladribin for treating LCH, this drug is also a potentially interesting treatment for sites of ECD in the CNS that are refractory to IFNα [8]. Dagna et al. recently reported the key role of TNFα in ECD and the efficacy of infliximab in two patients with this disease [16].

Pathophysiology

The understanding of the pathogenesis of ECD has improved since 2006. In an immunohistochemical study of three patients, Stoppacciaro et al. showed that a complex network of cytokines and chemokines regulates histiocyte recruitment and accumulation in the lesions [17]. Dagna et al. recently assessed both spontaneous and stimulated cytokine

production by mononuclear cells from the biopsy fragments of a single patient [18]. This study revealed that tumor necrosis factor α (TNFα) was produced after stimulation and described the spontaneous secretion of IL-6 and IL-8, a known chemoattractant for polymorphonuclear cells and monocytes. Aouba et al. showed, in two patients, that targeting the IL-1 pathway might be an appropriate strategy [15]. We recently analyzed 23 cytokines production in serum samples obtained from a large cohort of ECD patients [19]. Our data revealed intense systemic immune activation in these 37 patients, mostly involving IFNα, IL-1/IL1-RA, IL-6, IL-12 and MCP-1. These findings further highlight the importance of the disruption of the systemic immune Th-1–oriented response associated with this condition, providing clues to more focused therapeutic agents.

Impact of BRAF Mutations on Management

The mitogen-activated protein kinase (MAPK) has been implicated in the pathophysiology of many cancers, especially melanoma, lung and colorectal cancers. Under physiologic conditions, the RAS-RAF-mitogen activated protein kinase (MEK)-mitogen-activated protein kinase (ERK) signaling cascade interaction is initiated by ligation of a receptor-linked tyrosine kinase by its corresponding growth factor. BRAFV600E mutation is responsible for a constitutively active kinase. Vemurafenib – a selective low molecular weight BRAF kinase inhibitor effective for the treatment of metastatic melanoma, including cerebral metastases – has been shown to be highly effective for treating bone, retro-orbital, retroperitoneal and cardiac lesions in three ECD patients with mutations.

In 2012, we showed that *BRAF*^{V600E} gain-of-function mutations were present in 57 % of LCH cases and 54 % of ECD cases, but not in other types of histiocytosis, confirming the clonal nature of LCH and ECD in large subsets of patients [20]. Targeted therapy with an inhibitor of mutated BRAF — vemurafenib, a newly approved selective low molecular weight BRAF kinase inhibitor — improves survival in patients with melanoma including cerebral metastases. Vemurafenib selectively suppresses proliferation in tumour cells expressing mutated BRAFV600E proteins. We used vemurafenib to treat three patients with multisystemic and refractory ECD carrying the *BRAF*^{V600E} mutation, two of whom also had skin or lymph node LCH involvement [21]. Vemurafenib treatment led to rapid, substantial, clinical and biological improvement in all patients, and the tumor response was confirmed by positron emission tomography (PET), computed tomography (CT) and/or magnetic resonance imaging (MRI) 1 month after treatment initiation. The treatment was still effective after 4 months of follow-up, although persistent disease activity was still observed. Such short study was proof-of-concept in showing that BRAF mutation may play a direct role in the physiopathology of the disease. We believe that treatment with vemurafenib should be considered for patients with severe, refractory *BRAF*^{V600E} histiocytosis, particularly if the disease is life-threatening. An appropriate dosing schedule and treatment duration remain to be determined, but these findings provide compelling evidence that BRAF inhibition is rapidly effective against *BRAF*^{V600E}-associated ECD. The long-term efficacy of BRAF inhibition in ECD should also be studied, as secondary resistance develops in almost all cases of *BRAF*^{V600E}-associated melanoma.

Pulmonary Involvement in ECD

Prior to the 2009 review of the pulmonary aspects of ECD, only a few studies had assessed the frequency of pulmonary involvement in ECD. Evidence of such involvement was found in eight (14 %) of the 59 patients reported by Veyssier-Belot et al. [3]. In a previous review, 41 (23 %) of the 176 cases reported in articles published in English (up to June 2003) were also found to display pulmonary involvement [22].

In a subsequent MEDLINE search, we identified 72 (23 %) cases of clear-cut pulmonary involvement in 319 patients published between 1930 and November 2008 (23, Table 14.3). The prognosis was grim in some of these cases of pulmonary involvement sometimes complicated with fatal respiratory failure due to pulmonary fibrosis. However, data regarding pulmonary involvement were incomplete for many cases in these reports, highlighting the lack of recognition of pulmonary signs in ECD patients.

We reported our experience with pulmonary involvement, at a single center, for 34 consecutive ECD patients referred between 1981 and 2008 [23]. Data were obtained for 23 men and 11 women. Median age at diagnosis was 53.7 years (range: 16–73 years) and median follow-up was 3.5 years (1.4–5.3 years). Median age at onset was 51.1 years (6–70 years) and median age at ECD diagnosis was 53.7 years (16–73 years). Smoking status was treated as a dichotomous variable: patients who had never smoked ($n=21$), and former or current smokers ($n=13$). None of the patients was known to have any specific occupational exposure.

Only eight patients (26 %) experienced persistent pulmonary symptoms. Four patients (12 %) had chronic dyspnea, three patients (9 %) had a persistent dry cough and one patient (3 %) had both chronic dyspnea and a dry cough. Physical examination revealed crackles in two patients (6 %). None of the patients displayed cyanosis, finger clubbing or physical signs of pulmonary hypertension. Two patients had episodes of acute pulmonary failure (one had central hypoventilation secondary to CNS involvement; one had *Pneumocystis* pneumonia while on treatment with corticosteroids and IFNα).

Table 14.3 Main characteristics of the 72 patients with pulmonary involvement of ECD published in the medical literature

Case number	Authors	Year	Sex/age	Original case nb[a]	Respiratory clinical manifestations	Respiratory radiological findings	Histology	Follow-up	Others organs involved
1	Chester	1930	F/44	1	Dyspnea	NA	Autopsy	Death by heart failure	Eye, liver, skin
2	Heine	1934	M/50		NA	NA	Autopsy	NA	CNS, eye
3	Masshoff	1948	F/45		NA	NA	Autopsy	Death by dehydration	CNS
4	Cavanagh	1954	F/64	1	Dyspnea	Opacities of upper lobes	Autopsy	Death by heart failure	Bone, CNS, kidney, large-vessels, skin
5			F/49	2	None	NA	Autopsy	Death	Bone, CNS, kidney, large-vessels, skin
6	Elian	1969	M/40		NA	NA	Autopsy	Death	Skin, CNS
7	Jaffe	1972	F/54		NA	NA	NA	NA	NA
8	Resnick	1982	M/76	1	NA	Diffuse fibrosis	Autopsy	Death by sepsis	Bone, kidney
9	Alper	1983	M/65		Dyspnea	Diffuse fibrosis, pleural effusion	Autopsy – TBB – lung	Death by heart failure	Eye, liver, spleen, skin
10			F/40		NA	ILD, pleural effusion	Autopsy	Death by cerebral hemorrhage	CNS, eye, bone, skin
11	Palmer	1984	M/51		None	ILD	Retroperitoneal biopsy	Alive at 2 years	Bone, kidney, eye, liver
12	Sherman	1985	M/70	1	Dyspnea	NA	TBB – lung	Death	Eye
13	Freyschmidt	1986	F/60		NA	ILD	Autopsy	Death within 3 weeks	NA
14	Miller	1986	M/44		Cough, pleural pain	Pleural thickening	Skin, bone, liver	NA	Bone, skin, liver, spleen
15	Sandrock	1989	M/21	1	Dyspnea, pericarditis	Pleural infiltration	Pericardium	Alive	Heart, skin, bone, liver, spleen
16	Globerman	1991	M/7		None	Perivascular infiltration	NA	Alive	NA
17	Fink	1991	M/76		NA	Pleural effusion	Autopsy	Death by myocardial infarction	CNS, eye, bone
18	Kujat	1991	M/53		NA	ILD	Retroperitoneal biopsy	NA	CNS, kidney, skin
19	Schields	1991	M/38	1	NA	Pleural thickening	Eye	Death by heart and renal failures	Eye, kidney, skin
20	Athanasou	1993	M/72		NA	NA	Lung	NA	CNS, heart, bone
21	Remy-Jardin	1993	F/50		Dyspnea, crackles	ILD	TBB, lung, bone	Respiratory involvement worsening.	Eye, skin, bone, CNS, kidney, liver, spleen, large-vessels
	Madroszyk	1994							
	Caparros-Lefebvre	1995		3				Death by CNS involvement	
	Farre	1995		2					
22	Veyssier-Belot et al.	1996	F/50	3	Dyspnea	ILD	TBB, bone	Death by CNS involvement	Bone, eye, CNS
23	Devouassoux	1998	F/41		Dyspnea	ILD	Lung	NA	Bone

(continued)

Table 14.3 (continued)

Case number	Authors	Year	Sex/age	Original case nb[a]	Respiratory clinical manifestations	Respiratory radiological findings	Histology	Follow-up	Others organs involved
24	Egan et al.	1999	F/62	1	Cough, dyspnea	NA	Lung CD 68+/CD1a−	Death by pulmonary fibrosis	CNS
25			F/46	2	Cough, dyspnea	NA	TBB−/bone+/skin+	Stability	Skin, adrenal glands
26			F/25	3	Cough, dyspnea, pleural pain	NA	Lung CD68+/CD1a−, skin	NA	CNS, skin
27			F/65	4	Acute respiratory failure	NA	Lung CD 68+/CD1a−	NA	NA
28			H/70	5	Dyspnea	NA	Lung CD 68+/CD1a−	Stability	CNS
29	Rush	2000	M/71	1	Dyspnea	ILD, pleural thickening	Lung, bone	Death	Bone
30			M/63	2	Dyspnea, cough	Cysts, ILD, pleural thickening	Lung, osteomedullar biopsy	Death by respiratory failure	Bone, liver, spleen
31			F/69	3	Dyspnea	Pleural effusion and thickening, ILD	Lung, retro-orbital, autopsy	Death by respiratory failure	Bone, eye
32	Wittenberg	2000	NA		NA	8 patients with septal and scissural thickening, and ground glass opacities	Lung in 5 patients	NA	NA
33			NA		NA			NA	NA
34			NA		NA			NA	NA
35			NA		NA			NA	NA
36			NA		NA	4 patients with pleural effusion	Other unknown	NA	NA
37			NA		NA			NA	NA
38			NA		NA				
39			NA		NA			NA	NA
40	Dimonte	2001	M/36		Dyspnea	Thickening of interlobular septa, fibrosis of the peribronchial interstitium	Bone, pulmonary TBB	NA	Bone, CNS, heart, skin
41	Bourke	2003	M/55		Dyspnea	ILD, pleural thickening	Lung CD68+/CD1a−	Stability	NA
42	Bisceglia	2003	M/35		NA	NA	Bone CD68+/CD1a−	NA	Bone, CNS, skin
43			M/49		Respiratory insufficiency	NA	Transplantation	Lung transplantation	Bone
44			M/50		Dyspnea, pleural pain	Pleural thickening, centrilobular opacities	Lung CD68+/CD1a−	Lost of follow-up	NA
45	Kang	2003	F/53	3	Dyspnea, fever	Interstitial thickening, pleural effusion, pericarditis	Lung CD68+/CD1a−	Death by respiratory failure	Bone, kidney, eye
46	Caramaschi	2004	NA/71	1	NA	Pleural effusion, Pulmonary fibrosis	Bone	NA	Large-vessels, pericarditis, kidney, bone
47			NA	2	NA	Polyseritis, pulmonary fibrosis	Bone	Stability	CNS, large-vessels, bone, kidney

48	Clerico	2003	F/14		NA	Right pleural effusion, diffuse smooth interlobular septal thickening and right basal micronodular opacities	Bone, omentum	NA	Mammary gland, bone, abdominal, CNS
49	Allen et al.	2004	M/60		Dyspnea	Pleural thickening, ILD	Retro-orbital biopsy, lung CD68+	Respiratory status worsened/death within 5 months	Eye, bone, pericardium, kidney
50	Röpke	2004	M/40		Dyspnea	Pulmonary infiltrates	Retro-orbital	NA	Eye, skin
51	Chung	2005	F/53		Dyspnea	Interstitial thickening, ground glass opacities	TBB−/bone+/lung	Respiratory status worsened/Death	Pericardium, large-vessels, bone, kidney
52	Rao	2005	M/68		Cough, pleural pain	ILD, ground glass opacities, pleural thickening	Lung, bone, autopsy	Death within 3 months	Bone, liver, spleen, kidney, bladder
53	Krüger	2006	M/58		Dry cough, dyspnea	Pulmonary fibrosis	Lung	Stabilization after introduction of cyclophosphamide	Kidney, aorta, bone
54	Saboerali	2006	M/45		Chest pain, dry cough	Pleural effusion and thickening	Pleural, lung, autopsy	Death by heart failure	Kidney, mesentery, spleen, bone
55	Stoppacciaro et al.	2006	M/45	1	NA	NA	TBB	NA	CNS, eye, kidney
56			M/52	3	NA	NA	Lung	NA	CNS
57	Kong	2007	F/39		Cough, dyspnea, crackles	ILD	TBB−/bone+	Death by respiratory failure	Pericardium, bone
58	Busemann	2007	M/49		None	NA	Lung, bone marrow	Death by hemophagocytosis	Bone, kidney
59	Lau	2007	F/45		None	Streaky densities, fibrosis	Eye	Death by septic shock	Eye, bone, large-vessels, adrenal glands
60	Yano	2007	M/55		Dyspnea	NA	NA	Stability after cyclophosphamide	NA
61	Salsano	2008	M/60		NA	Pleural effusion	Kidney	NA	Bone, CNS, kidney, heart
62	Spyridonidis	2008	M/62		Dyspnea	Parenchymental involvement	NA	NA	Bone, eye
63	Granier	2008	M/65		NA	Lung fibrosis and pleural effusion	Lung, kidney, heart	NA	Lung, kidney, heart, CNS
64	Ferretti	2008	NA		NA	Focal air space consolidation	Lung	NA	NA

(continued)

Table 14.3 (continued)

Case number	Authors	Year	Sex/age	Original case nb[a]	Respiratory clinical manifestations	Respiratory radiological findings	Histology	Follow-up	Others organs involved
65	Garg	2008	F/60		Dry cough, dyspnea, bronchial breath sounds	ILD	Skin	NA	Skin, bone
66	Dickson	2008	F/77	2	Dyspnea	NA	Autopsy	Death by sepsis	CNS, heart
67	Loddenkemper	2008	M/54		Chest pain	Lung fibrosis	Bone marrow, kidney	Stability	Large-vessels, kidney
68	Mnif	2008	F/38		NA	Ground glass opacities	Kidney	NA	Bone, CNS, kidney
69	Nicholson	2008	M/72		Dyspnea	Pleural effusion and thickening, nodular reticular shadowing	Pleural biopsy	NA	Large-vessels, bone
70	Protopapadakis	2008	M/48		Dyspnea, cough	ILD	Lung	Death by cardiac and renal failure	Bone, heart, kidney, eye

NA non available data, *TBB* transbronchial biopsy, *ILD* interstitial lung disease

[a]Case number under which the patient was reported in the original publication

Imaging Features of ECD

Imaging plays a key role in the diagnosis and disease and evaluation of its extension. Some imaging features are specific enough to suggest a diagnosis of ECD. Furthermore, imaging often reveals asymptomatic organ involvement with potential prognostic and therapeutic consequences.

Thoracic evaluation is based on CT scan with contrast injection and cardiac gating.

Pleural involvement mostly consists of a thickening of the visceral pleura, sometimes associated with pleural effusion. Histiocytic infiltration may involve all the anatomic compartments, from the pleura to the retrocrural space and periaorta, sheathing the descending aorta and intercostal arteries (Fig. 14.1). CT findings of lung parenchyma involvement reflect the interstitial spread of the disease. Lesions may follow a lymphatic distribution including smooth thickening of the interlobular septa, peribronchovascular bundles and subpleural space. Centrilobular ill-defined micronodules, and ground-glass opacities, with a focal or diffuse distribution, may also occur (Figs. 14.2, 14.3 and 14.4). Localized honeycombing and fibrotic changes may be seen in zones of severe and extensive disease. The presence of isolated cystic lesions scattered throughout the non fibrotic lung (Fig. 14.5) raises questions about the relationship between ECD and LCH. Interestingly, associations of ECD and LCH have been reported [24], suggesting that both these types of proliferation may be derived from a common progenitor.

Pleural and parenchymal involvement is often associated with perivascular and mediastinal disease [25]. CT and MRI scans typically show periaortic soft-tissue infiltration, extending from the ascending aorta to the abdominal aorta and creating, in late-stage disease, a so-called "coated aorta" appearance. Sheathing of the aorta is circumferential, sometimes asymmetric, smooth and regular, without clear stenosis or thickening of the aortic wall itself. The periaortic

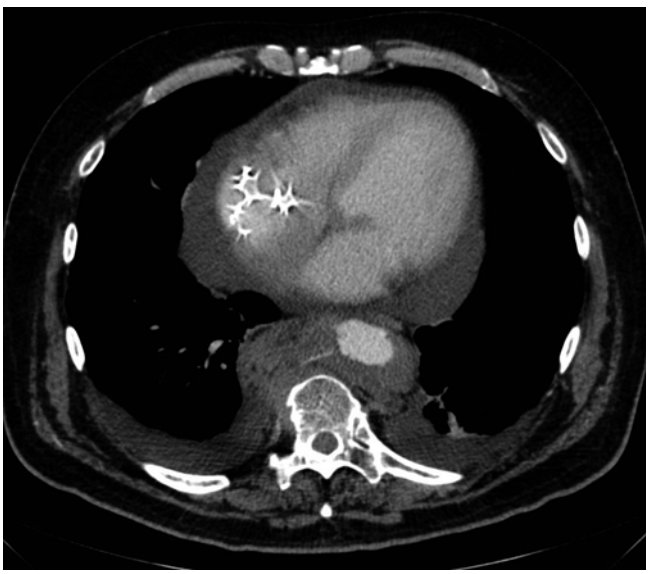


Fig. 14.1 Soft tissue infiltration sheathing the descending aorta and a right intercostal artery and extending towards the retrocrural space and visceral pleura. Pleural and pericardial effusions

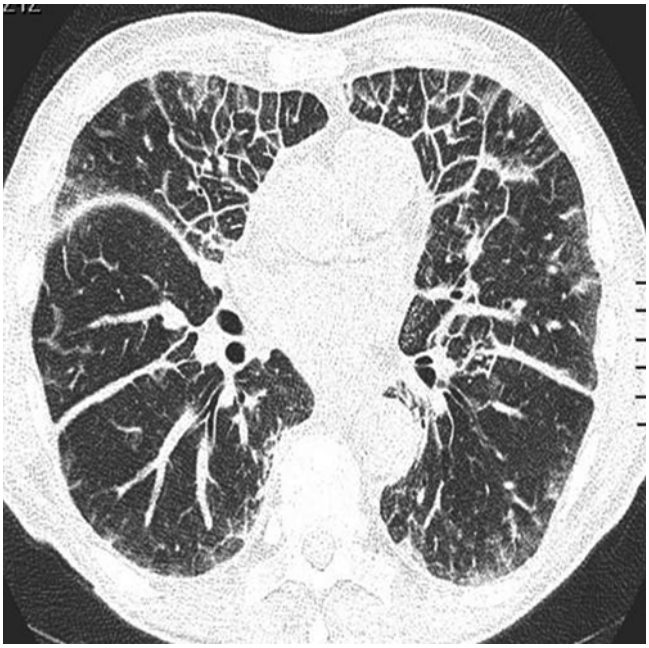


Fig. 14.2 Smooth and regular thickening of the interlobular septa in the anterior parts of the lungs, associated with thickening of the subpleural interstitium and ground glass opacities

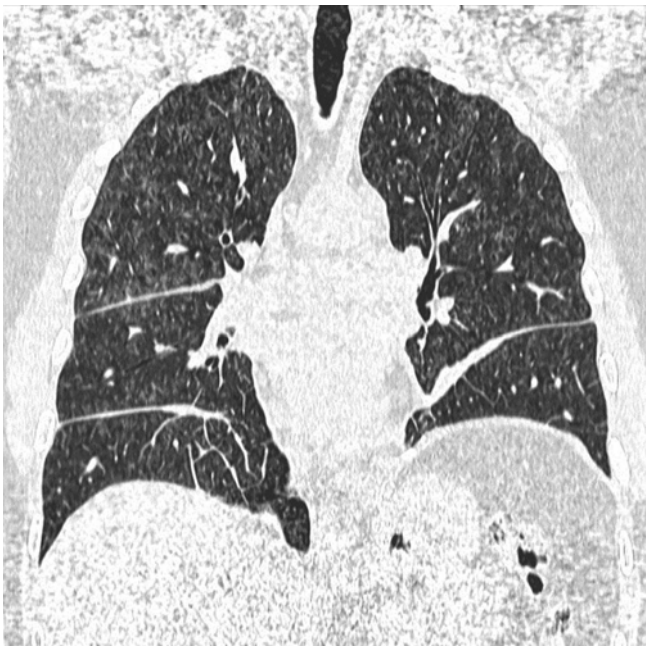


Fig. 14.3 Diffuse, centrilobular, ill-defined micronodules associated with thickening of the subpleural space, and smooth septal lines in the bases

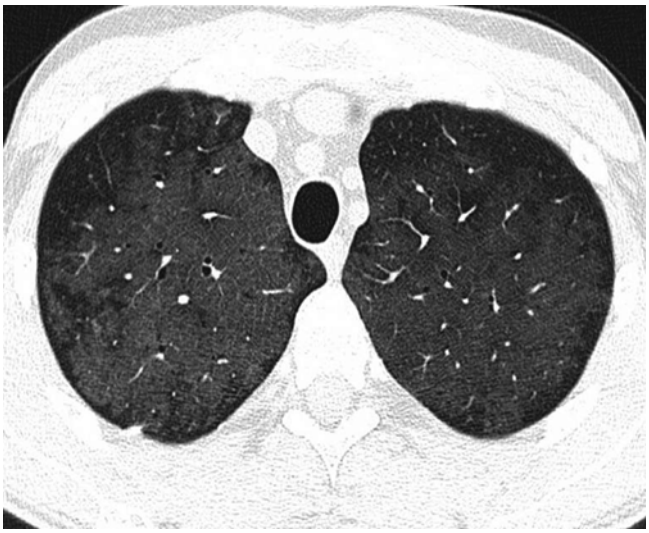


Fig. 14.4 Diffuse and homogeneous ground glass opacities superimposed on a weak reticular pattern

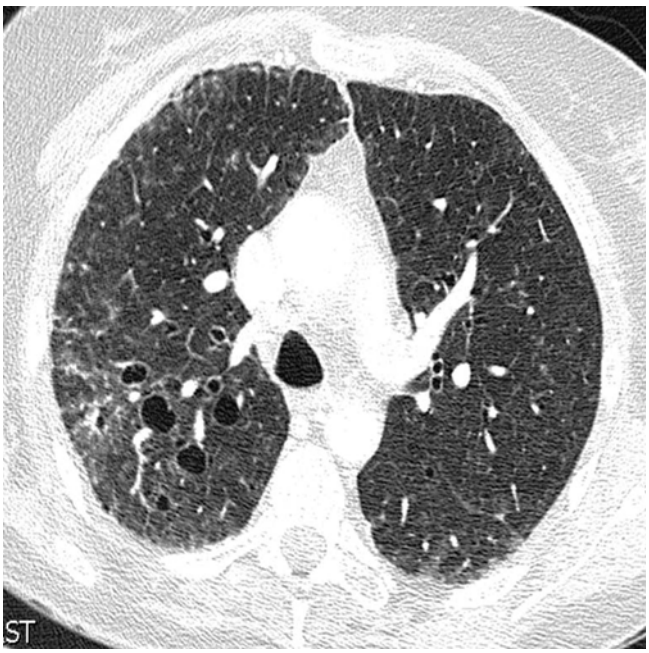


Fig. 14.5 Nodular and micronodular ground glass opacities in the lung apices, associated with a few anterior septal lines, and thin-walled cystic lesions

infiltration tends to spread to the areas around all aortic collaterals, including the supra-aortic trunks, intercostal, renal and coronary arteries. Specific infiltration of the right coronary sulcus surrounding the right coronary artery is frequent (approximately 55 % of cases), and is suggestive of ECD, even if isolated. Infiltration of the myocardium, particularly of the right atrium wall, may result in a pseudotumoral appearance. Mediastinal venous structures are generally respected, at least in the early stages of the disease. However, in cases of extensive mediastinal infiltration, the superior vena cava and the pulmonary trunk and main arteries may be sheathed, decreasing the vascular lumen.

Additional cardiac evaluations can be carried out by MRI and ultrasonography (US). On MRI, the soft-tissue infiltration is of a similar intensity to the muscle signal on T1- and T2-weighted spin-echo sequences, with slight, homogeneous enhancement after gadolinium injection. On CT, it appears as a soft, homogeneous tissue with slight and late enhancement after contrast injection.

Symmetric radiodensities in the metaphyseal and diaphyseal portions of long bones, and abnormally high levels of labeling in the long bones of the legs on technetium-99 (99Tc) bone scintigraphy are typical hallmarks of the disease [2]. This type of imaging for the detection of skeletal involvement has now been partly replaced by PET-CT. The sensitivity of PET-CT differs considerably between sites of involvement, but this technique is more effective during follow-up, to evaluate therapeutic response, than for initial assessment of the disease [26].

Imaging findings for individual lesions are not specific to ECD, but the presence of lesions at multiple sites is highly suggestive of ECD, particularly if the characteristic bone features are present.

Other Features (Including Lung Function, Cytology and Pathology), Treatment and Outcome Data in ECD Lung Involvement

Twenty-one (62 %) of the 34 patients underwent pulmonary function testing (PFT). PFT results were normal in 15 patients, whereas the remaining six patients (29 %) had a restrictive pattern [median total lung capacity (TLC): 89 %, 64–117 %]. Thirteen patients (38 %) had a diffusing capacity of the lung for carbon monoxide <80 % of the predicted value [median DLCO: 82.5 %, 59–133 %]. Arterial blood gas analyses were normal in all but one patient who had resting hypoxemia [median PaO_2 = 86.3 mmHg, range: 63.4–100 mmHg].

Bronchoscopy was performed routinely on all patients with suspected or proven interstitial lung disease, and was carried out in 12 patients (35 %) with interstitial pulmonary infiltrates on chest CT-scan. Six of these patients underwent endobronchial biopsy (EBB) and the other six underwent bronchoalveolar lavage (BAL) at least once. All EBB results were normal and none of the patients underwent transbronchial biopsy. Macroscopic observation of the BAL fluid revealed the presence of an opalescent fluid in all six of these patients. This finding of opalescent fluid in all the ECD patients undergoing BAL was a highly surprising finding. An opalescent appearance, presumably attributable to the presence of foamy histiocytes within the BAL fluid, could thus be used as a marker of pulmonary involvement in this disease.

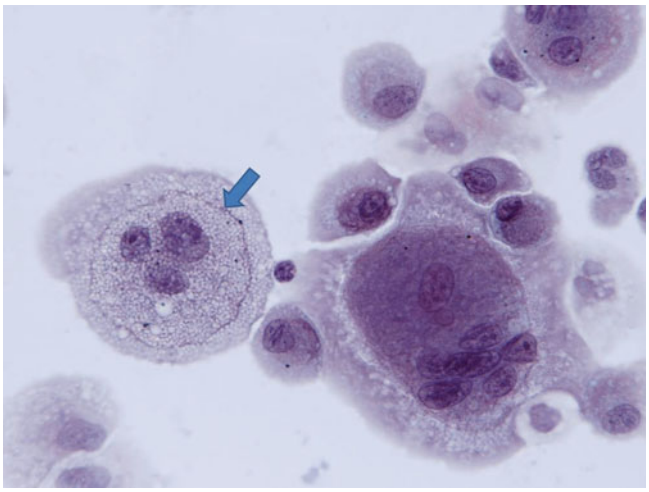


Fig. 14.6 Double-contoured histiocytes in the BAL fluid of patients with ECD. Presence of an intra-cytoplasmic membrane-like structure (*arrow*)

Our pulmonary pathologist (Frédérique Capron) also identified two atypical findings. One patient had double-contoured foamy histiocytes (Fig. 14.6), which have never been reported before. This finding warrants further studies, including electron microscopy, which could potentially provide valuable additional data. One patient had IgA plasmocytosis with predominant κ light chains in the BAL fluid. No open lung biopsy was performed in any of the patients, by contrast to previously published ECD case series [27].

Along with autopsy findings from the first cases described by Chester, the wedge biopsy of the lung was the main source of knowledge about the histopathological aspect of lung manifestations in ECD [27]. It should be noted that the combination of typical radiographic skeletal findings with the radiographic lung findings is highly suggestive of ECD, which generally makes wedge biopsy of the lung unnecessary. As suggested by medical imaging showing a lymphatic distribution of the lesions in the lung, the histiocytic infiltrate is mainly found in the visceral pleura, the interlobular septa, and around bronchovascular structures. Due to this lymphangitic pattern, the transbronchial biopsy cannot be diagnostic and is contraindicated in ECD [22, 27, 28]. The histiocytic infiltrate is made up of large histiocytes with a bland round or oval nucleus, and moderate to abundant cytoplasm that can be lightly eosinophilic or foamy. Multinucleate giant cells can be seen, some of them having the morphology of Touton's giant cells. Emperipolesis is generally not observed. The histiocytes could be intermingled with variable quantity of inflammatory cells such as small lymphocytes or plasma cells but without eosinophils. The fibrosis, the other major manifestation of ECD in the lung, has the same topographic distribution as histiocytic infiltrate. The fibrosis typically involves the pleura and interlobular septa but is much less pronounced in the interstitial inter-alveolar septa. It should be mentioned that, in some cases or some areas, due to the heterogeneous distribution of histiocytic infiltrate, the histiocytes can be very scarce within the fibrosis, which can make the diagnosis of ECD very difficult if small biopsies are performed.

Immunophenotypically, the histiocytes of ECD constantly express markers of macrophages such as CD68 (KP1) and CD163 [22, 28]. It is noteworthy that in contrast with CD163, CD68 (KP1) can be faintly expressed by histiocytes in ECD. Factor XIIIa, a marker of interstitial dendritic cells, is expressed in almost all cases tested. S100 protein is expressed in about 30 % of cases. In contrast to Langerhans cell histiocytosis, CD1a and CD207 (langerin) are constantly negative.

The differential diagnosis of ECD includes various histiocytic disorders that can involve the lung as follows:

- Histiocytic infiltrate in non-specific interstitial pneumonitis, bronchiolar obstruction, or any healing process;
- Reactive histiocytoses secondary to infectious agents (mycobacteria, malakoplakia, Whipple's disease);
- Crystal-storing histiocytosis,
- Storage diseases (Gaucher or Niemann-Pick disease),
- Proliferative histiocytic disorders (Langerhans cell histiocytosis or Rosai-Dorfman's disease), dendritic cell or histiocytic sarcoma.

The foamy macrophages, which can be seen in almost all these conditions, can be a cause of ECD overdiagnosis if other histological and clinical data are not taken into account.

In malakoplakia [29], Whipple's disease [30], and crystal-storing histiocytosis [31], the histiocytes have cytoplasmic characteristics which are easily distinguishable from those of ECD histiocytes. In malakoplakia, the histiocytes harbor cytoplasmic Michaelis-Gutmann bodies. Clinically, it manifests as a pulmonary nodule or pneumonia without lymphangitic distribution of the lesions. In lung, malakoplakia is usually associated with *Rhodococcus equi*, a Gram-positive coccobacillus, particularly in the context of HIV infection. In Whipple's disease, clinically significant lung involvement has been rarely documented. It is characterized by aggregates of foamy histiocytes containing periodic acid-Schiff-positive and Gram-positive granules. The diagnosis can rely on the detection of *Tropheryma whipplei* within the cytoplasm of macrophages by using immunostaining with a specific antibody.

Crystal-storing histiocytosis, which is related to plasma cell neoplasms, is characterized by accumulation of large histiocytes with intracytoplasmic eosinophilic immunoglobulin crystals.

In contrast to ECD, Gaucher cells infiltrate alveolar spaces, as well as inter-alveolar septa [32]. These cells exhibit a "wrinkled paper" appearance, highlighted with periodic acid–Schiff stain, and faintly expressed CD68.

Involvement of the lung by Niemann-Pick disease manifests as an endogenous lipid pneumonia consisting in an

alveolar filling by foamy cells with abundant finely vacuolated cytoplasm and eccentric nuclei [33].

In Rosai-Dorfman disease (RDD), histiocytes have large eosinophilic cytoplasm and exhibit a typical feature which consists in harboring intact lymphocytes within cytoplasmic vacuoles (i.e., emperipolesis) [34]. Moreover, plasma cell infiltrate is much more abundant than in ECD. Immunophenotypically, histiocytes of RDD are CD68+/PS100+ but are negative for markers of Langerhans cells, CD1a and CD207 (langerin), and the marker of interstitial dendritic cells, factor XIIIa. Topographically, RDD mainly concerns the large airways.

In Langerhans cell histiocytosis, the characteristic cells have a folded nucleus and abundant eosinophilic cytoplasm with indistinct cytoplasmic borders. They are intermingled with eosinophils. Immunophenotypically, Langerhans cells express CD1a, S100 protein and CD207 (langerin).

Dendritic cell malignant neoplasms and histiocytic sarcoma differ from ECD by the fact that the neoplastic histiocytes are pleomorphic and exhibit nuclear atypias and mitoses.

Twenty (59 %) of the 34 patients in a single center series had clinical and/or radiological evidence of pulmonary involvement, a much higher proportion than in previous studies. The wider availability of high-resolution chest CT-scan has increased the likelihood of detecting pulmonary involvement in the most recent ECD cases, and may also account for the higher occurrence of pulmonary involvement reported for recent large series.

Treatment with corticosteroids and/or IFNα resulted in a marked improvement of the pulmonary lesions in only one patient. No significant difference in survival was found between patients with and without pulmonary involvement ($p = 0.82$).

Finally, in a more recent review of 53 ECD cases published in 2011 [2], we detected pulmonary involvement in 43 % of cases. Thus, although the overall prognosis of the disease remains poor in some cases, pulmonary involvement, unlike CNS and cardiovascular infiltrations, does not appear to be a major prognostic factor in ECD.

The comparison of the characteristics of pulmonary ECD with those of LCH are presented in Table 14.4.

Rosai-Dorfman Disease (RDD)

Rosai-Dorfman disease (RDD), or sinus histiocytosis with massive lymphadenopathy, is a rare disease characterized by a benign proliferation of histiocytic cells within the sinus of the lymph nodes and the lymphatic vessels in cases of visceral involvement [35, 36]. This histiocytic disorder was first described in 1965 by Destombes [37]. It was subsequently identified as a unique clinicopathological entity in two publications dealing with four and 34 patients, respectively, by Rosai and Dorfman, in 1969 and 1972, under the name "sinus histiocytosis with massive lymphadenopathy" (SHML) [38, 39]. SHML has been reported in more than 700 publications on MEDLINE, but most of these articles report only limited numbers of cases. Rosai and Dorfman set up an international registry which, when published in 1990, included 423 distinct cases, and which remains, more than 20 years later, the main source of information about this condition.

RDD typically results in an enlargement of the lymph nodes (90 %), some of which may be extremely large, principally in the cervical region. Visceral damage is not rare. Diagnosis requires histologic examination: intrasinusal histiocytic proliferation with cells displaying emperipolesis or lymphocytophagocytosis. These histiocytes have a normal activated phenotype. Immunostaining is positive for CD68 and negative for CD1a, whereas staining for the S-100 protein is positive.

An association with immunological abnormalities or autoimmune events, such as autoimmune cytopenia in particular, is observed in less than 15 % of cases and is associated with a poorer prognosis.

The spontaneous clinical course of the disease is generally favorable. However, there is nevertheless a substantial risk of compression associated with large tumor masses, particularly in cases of retro-orbital or epidural involvement.

An abstention from treatment are generally recommended. Instead, treatment is reserved for cases of disease that is directly life-threatening, progressive, or in the presence of factors associated with a poor prognosis. Treatment, when indicated, is not codified and should be determined on a case-by-case basis at a specialist center. The options available are surgery, corticosteroids, cladribine, IFNα and tyrosine kinase inhibitors.

Respiratory tract involvement is rarely seen, in only 3 % of RDD cases with tracheal or broncheal infiltration and pulmonary fibrosis [40].

Imaging Features of RDD

Cervical lymph node involvement, resulting in massive bilateral lymphadenopathy, is the most characteristic finding in patients with RDD. The most common intrathoracic manifestation of RDD is the presence of mediastinal, hilar and/or peribronchial lymphadenopathies, which may compress the bronchial tree [41]. There is no specific imaging feature for the differentiation of lymphadenopathies in RDD from other diseases. These lymphadenopathies often display high levels of metabolism on ^{18}FDG-PET imaging and may develop calcifications (sometimes in an eggshell pattern) during treatment.

Table 14.4 Comparison of the characteristics of pulmonary Erdheim-Chester disease with those of Langerhans' cell histiocytosis

	Erdheim-Chester disease	Langerhans' cell histiocytosis
Epidemiology		
Sex	Slight male predominance	Slight female predominance
Age of onset	Any age (Mostly the fifth decade of life)	Any age (Mostly the third or fourth decade of life)
Risk factors	Unknown	Cigarette smokers (>90 %)
Involvement of the respiratory system		
Radiological findings	Smooth interlobular septal thickening	May vary depending on the stage of the disease : from early-stage nodules to cavitary nodules, to thick-walled cysts, and finally to thin-walled cysts
	Micronodules	Unusual pleural involvement
	Ground glass opacities	
	Thickening of interlobar fissures	
	Parenchymal consolidation	
	Frequent pleural involvement	
Pathological findings		
Birbeck granules	Absent	Present
CD1a	Negative	Positive
CD68	Positive	Positive
S100	Positive (20 %) or negative	Positive
Clinical course and prognosis		
	Pulmonary involvement does not appear to be a prognostic factor (High rate of fatal cardiovascular complications and CNS involvement)	Variable clinical course: 50 % stability 25 % improvement 25 % progression
Treatment		
	Interferon alpha (Efficacy of interferon alpha is probably limited in the pulmonary localizations of the disease)	Smoking cessation
	Alternative treatments (vemurafenib, cladribine) not evaluated for lung	Corticosteroid Vinblastine Cladribine Lung transplantation

Airway involvement consists of intraluminal, submucosal polypoid lesions of the nasal septum and tracheobronchial tree, sometimes associated with airflow obstruction. Tracheal pseudotumoral masses have been reported [42]. Patients with lung parenchymal involvement may present with interstitial lung disease mimicking nonspecific interstitial pneumonia [41].

Niemann-Pick Disease (NPD)

Niemann-Pick disease (NPD) types A and B are rare neurovisceral autosomal recessive lysosomal storage disorders caused by acid sphingomyelinase (ASM) deficiency. Niemann-Pick disease type A (NPD-A) is a progressive neurological disease causing death in early childhood, whereas Niemann-Pick disease type B (NPD-B) has a wider spectrum of clinical signs [43] and no neurological involvement. Enzyme replacement therapy with recombinant sphingomyelinase is currently being studied as a possible treatment for NPD-B. Six variants of NPD have been described to date, and NPD-B is the most frequently associated with lung involvement, a major cause of morbidity and mortality in patients of all ages with this subtype of the disease.

Mutations of the *SMPD1* gene cause NPD-A and NPD-B and are responsible for complete or partial ASM deficiency; mutations of *NPC1* and *NPC2* cause NPD-C, an entirely different disease.

NPD-B affects between 0.4 and 0.6/100,000 live births. Diagnosis is confirmed by the demonstration of a decrease in cell lysosomal enzyme activity (ASM), as the most frequent mutation is the homozygous ΔR608 mutation of the acid sphingomyelinase gene (SMPD1).

The largest series studied to date is that reported by McGovern et al. [44], which included 59 NPD-B patients: 53 % of the patients were male, 92 % were white, and the median age was 17.6 years. The R608del mutation accounted for 25 % of all disease alleles. Most patients initially

presented with splenomegaly (78 %) or hepatomegaly (73 %). Frequent symptoms included bleeding (49 %), pulmonary infections and shortness of breath (42 % each), and joint/limb pain (39 %). Almost all the patients had documented splenomegaly and hepatomegaly, together with interstitial lung disease. Many patients had low levels of platelets and high-density lipoprotein, high levels of low-density lipoprotein, very low-density lipoprotein, triglycerides, leukocyte sphingomyelin and serum chitotriosidase, and abnormal liver function test results.

Thus, the presence in a given patient of the trio of hepatosplenomegaly, pulmonary involvement and dyslipidemia should raise questions about the possibility of NPD-B and lead to a search for consanguinity, as the transmission of this disease is autosomal recessive. The diagnosis can be confirmed by ASM determinations in white blood cells and genotyping.

Pulmonary Involvement in NPD-B

Pulmonary involvement is frequent in NPD type B patients [45]. Infiltration of the alveolar septa, bronchial walls and pleura by lipid-laden macrophages may give an interstitial and reticular/nodular pattern on chest X rays. Characteristic findings on CT-scans include interlobular septal thickening, ground-glass opacities and small, sometimes calcified, micronodules (Fig. 14.7). Occasionally, the combination of a reticular pattern and ground glass opacities results in a "crazy paving" appearance. The lesions generally begin in basal areas and progress cranially. CT-scans may also show coronary artery calcifications in both children and adults, due to the abnormal lipid profiles associated with the disease.

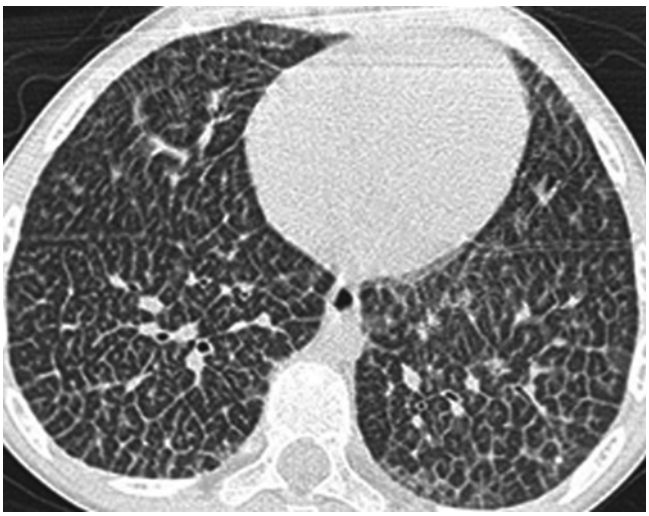


Fig. 14.7 Niemann-Pick disease type B: smooth thickening of the interlobular septa and centrilobular opacities reflecting the interstitial spread of the disease (Courtesy to R. Khayat)

The pulmonary involvement observed in NPD-B may result from a lack of catabolism of the surfactant responsible for diffuse endogenous lipid pneumonia. PFT shows a restrictive ventilatory pattern in 20 % of such cases, and a low DLCO in 70 % of cases. Other types of pulmonary involvement include bronchiolar infiltrations, which are associated with an obstructive ventilatory pattern on PFT in 33 % of cases. In their review of 53 NPD-B patients, Mendelson et al. [46] found abnormal chest X-ray results in 90 % of cases and chest CT-scans were abnormal in 97 % of cases.

ECD Criteria

The **following criteria** have been used to diagnose ECD in our 94 personal cases seen at our institution in December 2012 and for literature review observations[1]

(a) typical histologic findings: infiltration with foamy histiocytes nested among polymorphic granuloma and fibrosis or xanthogranulomatosis with CD68-positive and CD1a-negative immunohistochemical staining, which is typical of ECD histiocytes;

(b) typical skeletal findings[2] with (1) X-rays showing bilateral and symmetric cortical osteosclerosis of the diaphyseal and metaphyseal regions in the long bones and/or (2) symmetric and abnormally increased labeling of the distal ends of the long bones of the lower limbs, and sometimes the upper limbs, on 99Tc bone scintigraphy.

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[1]These ECD criteria were those used for our previous literature review published in 1996 [3] and 2004 [4].

[2]All our personal cases fulfill criterion (a) and all but 4 fulfilled criterion (b). The place of PET-CT has to be determined in future criteria for ECD diagnosis: in 2009 we reported a series of 31 ECD patients who had one or several PET-CT [26]; compared with the bone scintigraphy, the PET-CT yielded a sensitivity of 58.6 %, a specificity of 100 %, a PPV of 100 %, and an NPV of 14.3 %.

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Eosinophilic Pneumonia

15

Vincent Cottin and Jean-François Cordier

Introduction

The eosinophilic lung diseases (Table 15.1) 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.

Eosinophil Biology

Initially thought to be especially important in the defence against parasitic infestation, eosinophil leukocytes are now considered multifunctional cells implicated in innate and adaptive immunity, including but not restricted to numerous inflammatory reactions to parasitic helminth, bacterial, and viral infections [1]. Their broad role in homeostasis function, physiology, and pathophysiology is now well appreciated.

Eosinophil precursors differentiate and mature in the bone marrow under the action of cytokines and especially of interleukin (IL)-5, IL-3, and granulocyte-macrophage colony-stimulating factor (GM-CSF) [1, 2]. Activation of the ΔdblGATA-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, successively involving chemotaxis, adhesion, and diapedesis and processes, under the control of IL-5 and

Table 15.1 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 (Churg-Strauss syndrome)
Hypereosinophilic syndrome
Idiopathic hypereosinophilic obliterative bronchiolitis
Eosinophilic lung diseases of determined cause
Eosinophilic pneumonias of parasitic origin
Tropical eosinophilia
Ascaris pneumonia
Eosinophilic pneumonia in the 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 (toxic oil syndrome, L-tryptophan)
Eosinophilic pneumonia induced by radiation therapy to the breast
Miscellaneous lung diseases with possible associated eosinophilia
Organizing pneumonia
Asthma and eosinophilic bronchitis
Idiopathic interstitial pneumonias
Pulmonary Langerhans cell histiocytosis
Malignancies
Other

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eotaxin-1. In the tissues, they undergo apoptosis unless survival factors (mostly IL-5) are present.

The eosinophil contains two types of intracytoplasmic granules, the content of which can be released by degranulation, while other mediators are secreted (with involvement of vesicle-associated membrane proteins in the regulation of granule fusion within the cell). 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, 2]. 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 at electron microscopy by 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 on a molecular standpoint and are reviewed elsewhere [2]. In addition to cationic proteins, eosinophils release pro-inflammatory cytokines, lipid- and arachidonic acid–derived mediators, enzymes, reactive oxygen species, and matrix metalloproteases, all of which may contribute to the pathophysiology of eosinophilic lung diseases.

The eosinophil is involved in many allergic or inflammatory processes through its interaction with other cells, including especially T helper (Th) lymphocytes, but also mast cells and basophils, endothelial cells, macrophages, platelets, and fibroblasts. 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 synthetise 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 [3]. Overall, the paradigm of eosinophil function has changed from a terminal effector cell in allergic airway diseases to their being involved in the initial stages of pathophysiology.

Corticosteroids shorten eosinophil survival in the blood and tissues, and are currently 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), those are the target of several drugs in development, which can potentially change dramatically the therapeutic landscape of eosinophilic disorders in the near future [4]. Other promising targets for therapy include the IL-5 receptor, CD2 binding protein, IgE, and IL-4/IL-13 receptor, with a few agents already at the stage of clinical evaluation. Although histopathologic lesions in eosinophilic pneumonias are largely reversible, tissue damage can occur especially in allergic bronchopulmonary aspergillosis (ABPA), and in eosinophilic granulomatosis with polyangiitis (EGPA) (Churg-Strauss syndrome, CSS), with possible remodeling and fibrosis in the bronchial mucosa. It is unknown yet whether anti-IL-5 antibodies and other therapeutic agents that target eosinophil-specific molecules, may prevent tissue damage. In addition, newer drugs specifically targeting cytokines of the eosinophil lineage contribute to a better understanding of the pathogenic role of eosinophils [4].

General Features of Eosinophilic Pneumonias

Historical Perspective

Early descriptions of pulmonary "infiltration with eosinophilia" [5], of "pulmonary eosinophilia" [6], and later of "cryptogenic pulmonary eosinophilias" [7] included cases now considered as probable idiopathic chronic eosinophilic pneumonia (ICEP), EGPA, and Löffler's syndrome. Carrington and colleagues [8] described in 1969 the syndrome of ICEP.

Clinical Presentation

Eosinophilic pneumonia is a pneumonia where the eosinophils are the most prominent inflammatory cells on histopathologic examination, whereas infiltration with lymphocytes and neutrophils is moderate. 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 the 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 exposure.

Most eosinophilic pneumonias can be classified within one of the well-characterized and individualized syndromes. They may manifest by different clinicoradiologic syndromes, namely Löffler's 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 vast majority of cases of eosinophilic pneumonia respond dramatically to corticosteroid treatment 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 [7–9]. 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; presence of parasites or fungal hyphae in eosinophilic pneumonia of parasitic origin).

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 [8]. 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 palisading arrangement). Degranulated eosinophils can be identified within the site of eosinophilic pneumonia by electron microscopic or immunohistochemical studies [10]. Areas of non-prominent organization of the alveolar inflammatory exudate are common [8]. Mucus plugs obstructing the small airways may be present in ICEP [8] 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, intra-alveolar fibrinous exudates, organizing pneumonia, and non-necrotizing vasculitis [11].

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 or (preferably) in the lung.

Surgical or video-assisted thoracoscopic lung biopsy is seldom necessary. Although they can show characteristic features of eosinophilic pneumonia, transbronchial lung biopsies are generally not recommended due to the small size of the specimen that allows only partial morphologic evaluation. Bronchoalveolar lavage (BAL) is now considered 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 pneumonia at lung pathology. In normal subjects, BAL eosinophilia is lower than 1 % of cells at 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 [12, 13], and a cutoff of 25 % has been proposed for the diagnosis of IAEP [14]. 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 (with greater specificity when greater than 40 %).

Blood eosinophilia or hypereosinophilia 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 thus be done before starting corticosteroids. *Blood eosinophilia* is defined by an eosinophil blood count greater than 0.5×10^9/L, and *hypereosinophilia* by an eosinophil blood count greater than 1.5×10^9/L on two examinations at least 1 month interval, and/or tissue hypereosinophilia [15]. Blood eosinophilia greater than 1×10^9/L (and preferably hypereosinophilia) may obviate the need to perform BAL in individual cases with typical presentation. For example, BAL may occasionally be omitted to confirm Löffler's syndrome (as it occurs in ascariasis) in a patient with 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 disease), and BAL is recommended to confirm the diagnosis of eosinophilic pneumonia in most cases.

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 an 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 [8], in a series of nine patients, and was further confirmed and detailed by several and numerous case reports.

Clinical Features

ICEP predominantes in women with a 2:1 female-to-male ratio [9, 13], with a peak of incidence in the fourth decade [9], and a mean age of 45 years at diagnosis [13]. A majority of patients with ICEP are nonsmokers [9, 13], suggesting that smoking might be protective. About half of the patients have a history of atopy [9, 13] and up to two thirds have a history of asthma [9, 12, 13, 16, 17], with no particularities in the clinical presentation of ICEP with the exception of higher total immunoglobulin (Ig) E levels in asthmatics [12]. In addition, asthma may develop concomitantly with the diagnosis of ICEP (15 % of patients) or develop after ICEP (about 15 % of patients) [12]. Asthma in patients with ICEP often gets worse and requires long-term oral corticosteroid treatment [12].

ICEP is characterized by the progressive onset of cough, dyspnea, and chest pain [9, 13], with a mean interval between the onset of symptoms and the diagnosis of 4 months [13]. Mechanical ventilation may be required on exceptional occasion. Hemoptysis is rare but can occur in up to 10 % of cases [9, 13]. Chronic rhinitis or sinusitis symptoms are present in about 20 % of patients [13]. At lung auscultation, wheezes are found in one third of patients [9] and crackles in 38 % [13]. 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 [8, 9, 13, 18, 19] consist of alveolar opacities with ill-defined margins, with a density varying from ground-glass to consolidation (Fig. 15.1), and are migratory in 25 % of patients [13]. 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 [9], however peripheral and upper zone predominance of abnormalities is usually present.

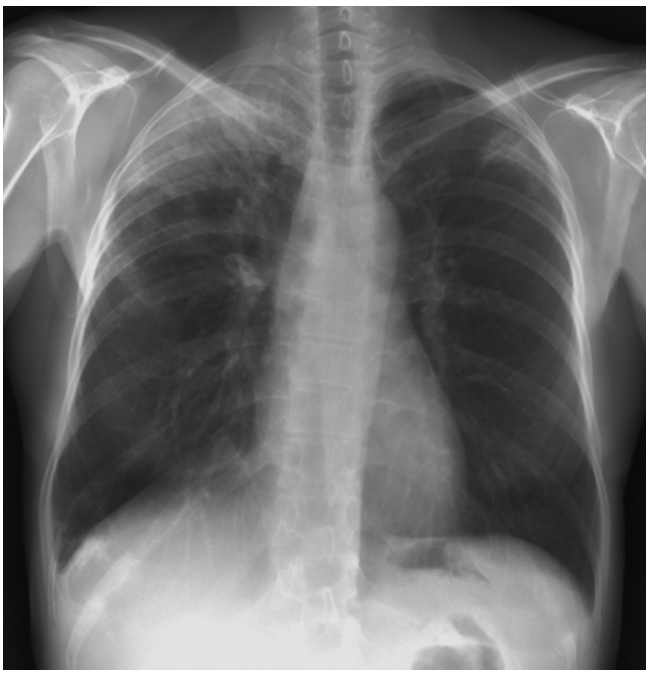

Fig. 15.1 Chest radiograph of a patient with idiopathic chronic eosinophilic pneumonia showing peripheral alveolar opacities predominating in the right upper lobe

Whereas the opacities are bilateral in at least 50 % of cases at chest x-ray [9], the proportion of bilateral opacities increases up to more than 95 % at high-resolution computed tomography (HRCT) [13] (Fig. 15.2). Predominance of ground-glass attenuation and consolidation in the periphery and upper lobes of the both lungs [9, 13] is very suggestive of ICEP [13, 19, 20]. Septal line thickening is common [20]. Centrilobular nodules (less than 20 % of cases) [19], 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 that is very suggestive of organizing pneumonia is rare contrary in ICEP. Pleural effusions (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 [13].

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 our series [13]. Eosinophils represent 26–32 % of the total blood leukocyte count [9, 13]. C-reactive protein level is elevated [9, 13]. Total blood IgE level is increased in about half of cases and greater than 1,000 kU/L in 15 % [13]. Antinuclear antibodies may occasionally be present [13]. Urinary EDN level indicating active eosinophil degranulation is markedly increased [21].

Bronchoalveolar Lavage

BAL eosinophilia is constant and key to the diagnosis of ICEP, obviating the need for lung biopsy in the vast majority of cases (Table 15.2). The mean eosinophil percentage at BAL differential cell count was 58 % at diagnosis in the series from our group [13], however the eosinophil count drops within a few days upon corticosteroid treatment. The percentage of neutrophils, mast cells, and lymphocytes a BAL may also be increased [13]. Sputum eosinophilia may also be present.

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 [3].

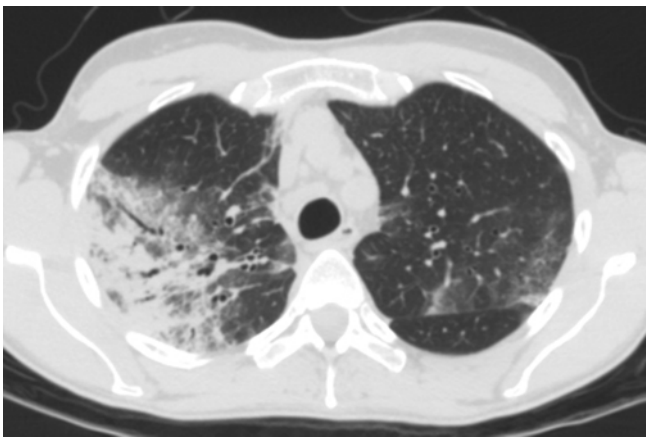

Fig. 15.2 Computed tomography (CT) scan of a patient with idiopathic chronic eosinophilic pneumonia showing bilateral asymmetric peripheral alveolar opacities with airspace consolidation and ground glass opacity

Differential Diagnosis

Extrapulmonary manifestations when present should challenge the diagnosis of ICEP and especially to consider 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 [8, 13]. 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 [9, 13], and a restrictive ventilatory defect in the other half [13]. The CO transfer factor is decreased in half of patients, and the transfer coefficient in about one fourth. Hypoxemia (PaO_2 <75 mmHg) present in two thirds of patients [13] may be due to right-to-left shunting in consolidated areas of the lung, as suggested by increased alveolar-arterial oxygen gradient [9]. With treatment, the lung function tests rapidly return to normal in most patients [9]. However, a ventilatory obstructive defect may develop over years in some patients, especially those with a markedly increased BAL eosinophilia at initial evaluation [22].

Treatment and Prognosis

Because most patients receive corticosteroids, the natural course of untreated ICEP is not well known [9]. However, spontaneous resolution of ICEP may occur [9, 13]. The clinical and radiologic response to corticosteroids is dramatic, with improvement of symptoms within 1 or 2 weeks and even within 48 h in about 80 % [13] of cases, and rapid clearance of pulmonary opacities at chest x-ray. In one series, the

Table 15.2 Diagnostic criteria for idiopathic chronic eosinophilic pneumonia

1. Diffuse pulmonary alveolar consolidation with air bronchogram and/or ground glass opacities at chest imaging, especially with peripheral predominance;
2. Eosinophilia at BAL differential cell count ≥40 % (or peripheral blood eosinophilia ≥1.0×10^9/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)

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 [13]. 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. 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 corticosteroids treatment [9, 13]. Relapses respond very well to corticosteroid treatment, that usually can be resumed at a dose of about 20 mg/day of prednisone [13].

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 [13]. Relapses of ICEP must be distinguished from asthma symptoms, and are less frequent in asthmatics, possibly because of inhaled corticosteroids prescribed after stopping oral corticosteroids [12, 13]. Inhaled corticosteroids might thus help in reducing the maintenance dose of oral corticosteroids, although they are not effective enough when given as monotherapy [23]. Long-term steroid use may lead to osteoporosis. 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 [24, 25]. The anti-IL-5 monoclonal antibody mepolizumab has not yet been evaluated in patients with ICEP.

Idiopathic 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 [11, 14, 17, 26–29] 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. As AEP can also be due to drug exposure or infection, known causes of acute eosinophilic lung disease must be excluded for the diagnosis of IAEP to be made (Table 15.3).

Clinical Features

IAEP may present at any age [30], however the mean age at presentation is around 30 years [14, 30], with a very strong predominance in males [29]. Most patients have no prior asthma history [17]. 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 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 [29, 31]. 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 [29, 31]. Flavoring components of smoked cigars have been suspected. In addition, the onset of IAEP seem 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 [14, 30, 32].

IAEP develops acutely or subacutely over less than 1 month in previously healthy individuals, with cough, dyspnea, fever, and chest pain at presentation [11, 30]. More than half of patients present with acute respiratory failure [29]. Abdominal complaints and also myalgias can occur [14]. Clinical signs include crackles or, less often, wheezes, and tachypnea and tachycardia.

Imaging

Imaging of patients with IAEP is quite distinct from those with ICEP. In addition to bilateral alveolar and/or interstitial opacities (Fig. 15.3) [14, 27, 28, 30], the chest x-ray commonly shows bilateral pleural effusion and Kerley B lines [14]. The chest x-ray returns to normal within 3 weeks [14, 30], with pleural effusions being the last abnormality to disappear [14]. Typical computed tomography (CT)

Table 15.3 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 ≤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)

abnormalities include ground-glass attenuation and air space consolidation (Fig. 15.4), 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 [14, 18, 27, 30, 33] (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 disease [14, 17, 30], a retrospective finding very suggestive of IAEP. Eosinophilia is also present at pleural fluid differential cell count [14] and in the sputum [17]. The IgE level may be elevated. Serum levels of thymus and activation-regulated chemokine (TARC/CCL17) (and other biomarkers including KL6 and exhaled nitric oxide) are often increased in IAEP, however lack of specificity of this finding does not rule out acute lung injury or infectious pneumonia [34, 35].

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 generally obviates the lung biopsy, at least in immunocompetent patients The average percentage of eosinophils at BAL differential count varies between series (37 % [14] to 54 % [30]), and lymphocyte and neutrophil counts can be moderately increased. 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), e.g. acute onset of respiratory failure not fully explained by cardiac failure or fluid overload (with objective exclusion of hydrostatic edema), bilateral opacities (not fully explained by effusions, lobar/lung collapse, or nodules), and a PaO_2/FiO_2 [fractional inspired oxygen concentration]

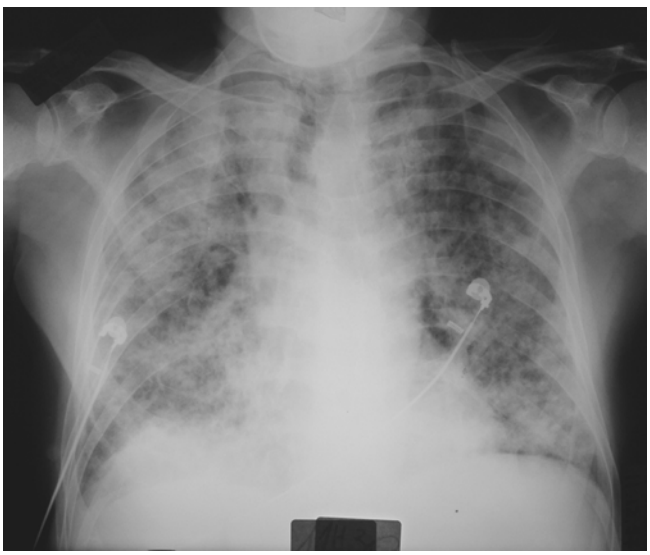

Fig. 15.3 Chest radiograph of a patient with idiopathic acute eosinophilic pneumonia and acute respiratory failure showing diffuse alveolar consolidation

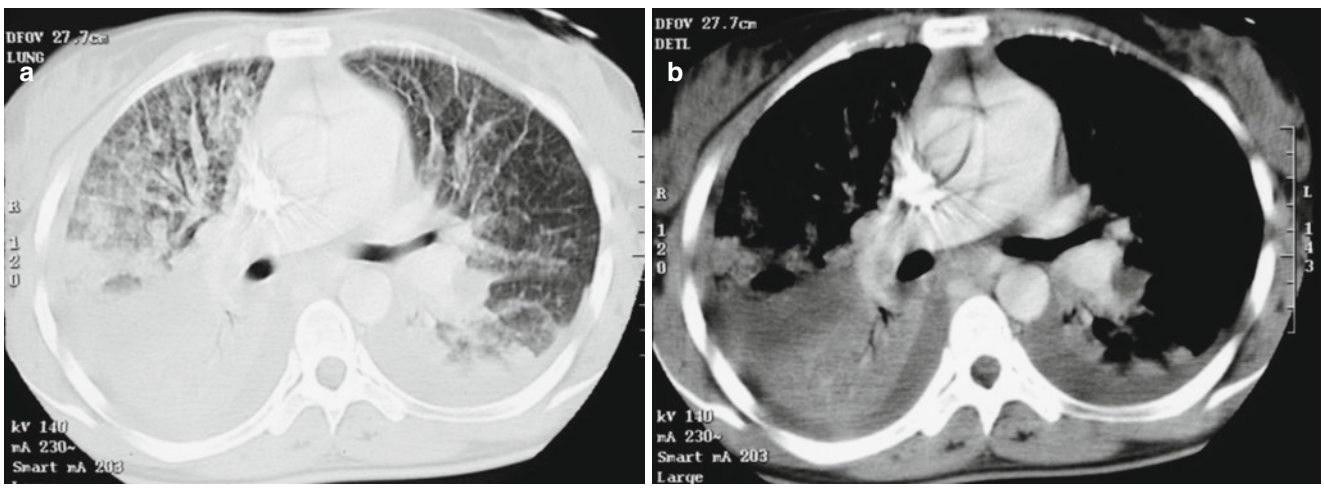

Fig. 15.4 CT scan of a patient with idiopathic acute eosinophilic pneumonia showing bilateral diffuse alveolar consolidation with air bronchogram and ground-glass opacity (a, parenchymal window) and bilateral mild pleural effusion (b, mediastinal window)

Table 15.4 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 % of smokers	2/3 of smokers, 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 Predominance in upper lobes and lung periphery	Bilateral patchy areas of ground glass attenuation, airspace consolidation, interlobular septal thickening, bilateral pleural effusion
Relapse	Yes, possibly multiple	No

<300 mmHg with positive end-expiratory pressure or continuous positive expiratory pressure ≥5 cm H_2O [36]. However, shock is exceptional and extrapulmonary organ failure does not occur in IAEP, in sharp contrast with IAEP.

Hypoxemia is associated with right-to-left shunting in areas with consolidation, and may be refractory to breathing 100 % oxygen in some patients [26, 30]. Alveolar-arterial oxygen gradient is increased [14]. Although mechanical ventilation was necessary in a majority of patients in earlier series [14, 30], more recent series have shown that the severity of IAEP is more varied than originally reported [29].

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 [14].

Lung Biopsy

Lung biopsy is 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 [11, 14, 37].

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 [30, 34], and therefore improvement concomitant with corticosteroid treatment is not a diagnostic criterion of IAEP. In most patients diagnosed with IAEP, a corticosteroid treatment is initiated, with initially intravenous methyl prednisolone later changed to oral prednisone or prednisolone that can be tapered over 2–4 weeks [14]. FiO_2 may be decreased within a few hours of corticosteroid treatment in many patients initially requiring oxygen [14]; most patients are rapidly weaned from the ventilator. The clinical improvement begins within 3 days [29]. 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 [29]. 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) [29]. No relapse occurs after stopping corticosteroid treatment, in contrast with ICEP (Table 15.4).

No significant clinical or imaging sequelae persist on 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 resuming of cigarette smoking after smoking cessation.

Eosinophilic Granulomatosis with Polyangiitis (Ex Churg-Strauss Syndrome)

History and Nomenclature

The first reliable case of EGPA was reported by Lamb in 1914 [38]. Churg and Strauss described in 1951 [39] the eponymous syndrome of “allergic granulomatosis, allergic angitiis, and periarteritis nodosa”, mainly from autopsied cases. In the 1992 Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis [40], 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 [41], 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 microspic polyangiitis and granulomatosis with polyangiitis (Wegener’s), 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 [41]. The disease may be confined to a limited

number of organs especially the upper or lower respiratory tract [41]. The terminology of EGPA underscores that it is indeed a vasculitis, although not all patients have robust criteria of documented systemic vasculitis or ANCA [42]. The current terminology and classification likely requires further refinement.

Pathology

The pathologic lesions of EGPA (CSS) observed in recent series [43, 44] only rarely comprise all the characteristic features on biopsies from organs other than the lung, which is now rarely biopsied. The diagnosis is made earlier in the course of 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, the 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 [45, 46], with cases occasionally reported in children and adolescents. Asthma occurs at a mean age of about 35 years [45], preceding the onset of vasculitis by 3–9 years [45, 47–49]; therefore the mean age at diagnosis of EGPA ranges from 38 to 49 years [45, 49]. The interval between asthma and the onset of vasculitis may be much longer in rare cases [47], or they may be contemporaneous [49]. 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 [45, 47].

Chronic rhinitis (75 % of cases) [45], relapsing paranasal sinusitis (60 %) [48], and nasal polyposis with eosinophilic infiltration at histopathology are frequent. 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 the 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 [45–50]. Heart involvement mostly results from eosinophilic myocarditis, and rarely from arteritis of the larger coronary arteries [51, 52]. 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 strict cardiac evaluation is therefore warranted in any patient with suspected EGPA, generally including electrocardiogram, echocardiography, serum level of troponin, and magnetic resonance imaging of the heart. Cardiac MRI frequently shows late enhancement of the myocardium [53–55], which may correspond to myocarditis, however the absence of a gold standard, it is difficult at a given point in time 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, troponine level, 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 [56] is increased in patients with EGPA. Endomyocardial involvement (typically seen in idiopathic HES) is uncommon in EGPA.

Mononeuritis multiplex, present in 77 % of patients [48], 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. Digestive tract involvement (31 % of cases [48]) consists in 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[48]) mainly consist of palpable purpura of the extremities (Fig. 15.5), subcutaneous nodules (especially of the scalp and extremities), erythematous rashes, and urticaria. Renal involvement (about 25 % of cases) consists in mild severity glomerulonephritis or glomerular hematuria [48], however renal failure is rare contrasting with the other ANCA-associated vasculitides.

Imaging

Pulmonary opacities corresponding to eosinophilic pneumonia are present on chest x-ray in a majority of patients with EGPA (37 % [48] to 72 % [45, 57]) and consist of ill-defined opacities, sometimes migratory, transient, and of varying density [45, 47, 58, 59]. 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 CT, ground-glass attenuation and air space

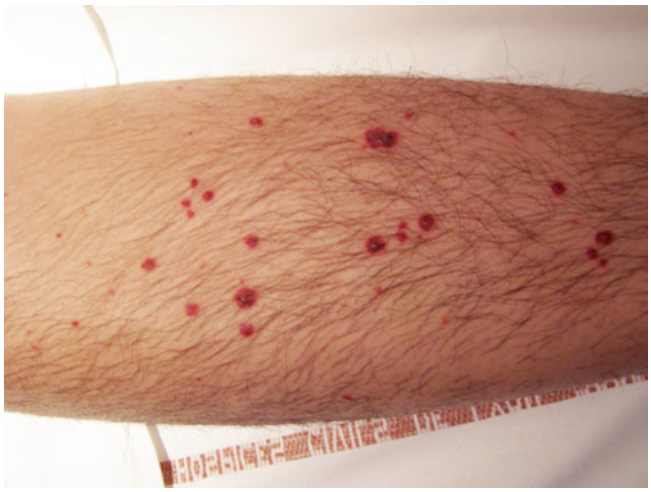

Fig. 15.5 Palpable purpura of the forearm in a patient with eosinophilic granulomatosis with polyangiitis

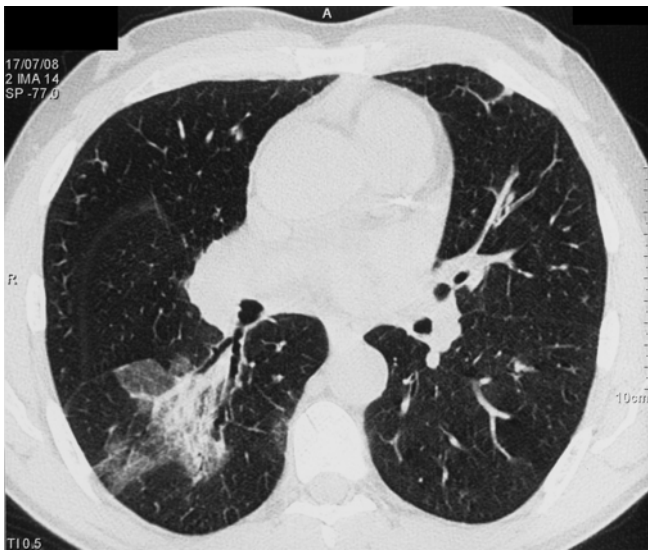

Fig. 15.6 CT scan of a patient with eosinophilic granulomatosis with polyangiitis showing airspace consolidation and ground-glass opacity in the right lower lobe

consolidation predominate, with peripheral or random distribution (Fig. 15.6). Bronchial wall thickening or dilation, interlobular septal thickening, hilar or mediastinal lymphadenopathy, pleural effusion, or pericardial effusion [18, 58, 59] are less commonly found. In one study, centrilobular nodules were more frequent in EGPA than in patients with ICEP [19]. However, EGPA is difficult to differentiate from other causes of eosinophilic lung diseases on the basis of HRCT imaging [18]. Importantly, pleural effusion when present may correspond to either inflammatory eosinophilic exudate directly related to EGPA or to a transudate caused by cardiomyopathy.

Laboratory Studies

Peripheral blood eosinophilia is a major feature of EGPA, with generally eosinophil counts comprised between 5 and 20×10^9/L and occasionally higher values [45, 47, 48]. Blood eosinophilia usually parallels disease activity, and disappears within hours after the initiation of corticosteroid treatment. 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 rarely cytoplasmic ANCAs (c-ANCA) with proteinase 3 specificity [48, 49, 60–62]. Although nonspecific and not validated as useful biomarkers, the serum IgE level, the erythrocyte sedimentation rate, and the C-reactive protein level, and serum levels of IgG4, CCL17/TARC, and CCL26/Eotaxin-3 are increased. Anemia is common. High levels of urinary EDN may represent an activity index of disease.

Pathogenesis

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 progression of disease, and supporting an immunological hypothesis of disease. Furthermore, clonal $CD8^+/V\beta^+$ 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-beta gene rearrangement. Patients carrying the major histopathology complex DRB4 allele, involved in acquired specific immunity, are prone to develop EGPA. Familial EGPA has been reported.

Contrasting 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. When present in EGPA, allergy mainly consists of perennial allergies to *Dermatophagoides,* whereas seasonal allergies are less frequent than in the general asthmatic patient [63].

Some vaccines or desensitization may trigger or play a role as adjuvant factors [64]. Other possible triggering factors include *Aspergillus,* allergic bronchopulmonary candidiasis, *Ascaris,* bird exposure, or smoked cocaine. Some drugs have been suspected to induce EGPA, especially sulfonamides (used together with antiserum), diflunisal, macrolides, diphenylhydantoin, and more recently the anti-IgE antibody omalizumab [65]. In addition, leukotriene-receptor antagonists (montelukast, zafirlukast, pranlukast) have been suspected to be involved in the development of EGPA, although their role is controversial [49, 66–70]. The occurrence of EGPA is more frequent in patients receiving leukotriene receptor antagonists, however there is conflicting evidence whether the association is coincidental, whether some cases of smoldering EGPA flare

because of reducing oral or inhaled corticosteroids, or whether these drugs really exert a direct facilitating or triggering role on the vasculitis [24, 68]. A possible mechanistic link has been proposed [71]. Since EGPA may follow montelukast treatment in asthmatic patients without smoldering EGPA, may recur on rechallenge with the drug, and may remit on its withdrawal [66, 68], a causal relationship cannot be excluded [70], and we advocate that leukotriene receptor antagonists be avoided in patients with asthma, eosinophilia, and/or established or smoldering extrapulmonary manifestations.

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. Diagnosing EGPA may be challenging in patients with early disease corresponding to the so-called *formes frustes* [72], 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 [45] 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, however those do not include ANCAs, which when present do contribute to the diagnosis. Classification criteria (which are not *diagnostic* criteria) have been proposed by the American College of Rheumatology [73] (Table 15.5), but they cannot be readily used for diagnosis in an individual with suspected EGPA. Provisional diagnostic criteria including ANCA have been recently proposed [42]. Although a pathologic diagnosis is desirable and can be obtained from the skin, nerve, or muscle [48], it is

Table 15.5 Diagnostic and classification criteria of eosinophilic granulomatosis with polyangiitis

Lanham and colleagues [45]
Asthma
Eosinophilia
Evidence of vasculitis involving at least two organs
American College of Rheumatology [73]
Asthma
Eosinophilia >10 %
Mononeuropathy, or polyneuropathy
Pulmonary infiltrates, nonfixed
Paranasal sinus abnormality
Extravascular eosinophil infiltration on biopsy findings
NB 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
1992 Chapel Hill Consensus conference definition [40]
Eosinophil-rich and granulomatous inflammation involving the respiratory tract
Necrotising vasculitis affecting small-to-medium-size vessels
Asthma
Eosinophilia
2012 Chapel Hill Consensus conference definition [41]
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.
ANCA is more frequent when glomerulonephritis is present.
Diagnostic criteria used by these authors [42]
1. Asthma
2. Peripheral blood eosinophilia >1,500/mm^3 and/or alveolar eosinophilia >25 %
3. Extrapulmonary clinical manifestations of disease (other than rhinosinusitis), with at least one of the following:
Systemic manifestation typical of the disease: mononeuritis multiplex; or cardiomyopathy confidently attributed to the eosinophilic disorder; or palpable purpura;
Any extrapulmonary manifestation with histopathological evidence of vasculitis as demonstrated especially by skin, muscle, or nerve biopsy;
Any extrapulmonary manifestation with evidence of ANCA with antimyeloperoxidase or antiproteinase 3 specificity
NB When a single extrarespiratory manifestation attributable to the systemic disease is present, disease may be called "forme fruste *of Churg-Strauss syndrome"*

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 (See Clinical Vignette). Conversely, lung biopsy either transbronchial or video-assisted is seldom done.

Clinical Vignette

A 32-year old female, never-smoker, with a 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. 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 was further diagnosed with mononeuritis multiplex. The chest radiograph showed areas of ground glass opacity, with further patchy peripheral bilateral alveolar consolidation at chest CT. Peripheral blood eosinophils were 5.6×10^9/L. 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 per day for 1 month then progressively tapered). Montelukast was discontinued. Complete remission was obtained. Three years later, the patient 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. Peripheral blood eosinophils are in the normal range. There are no sequelae of systemic manifestations.

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 [8]. EGPA can also overlap with idiopathic HES. When present, ANCA or the finding of a 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.

In addition to contribute to the diagnosis of vasculitis, the presence (in 40 % of cases) or absence (in 60 % of the cases) of ANCAs is associated with distinct clinical phenotypes in EGPA [61, 62, 74] (Table 15.6). Patients with ANCA have a *vasculitic phenotype* of disease with an increased frequency of extracapillary glomerular lesions, peripheral neuropathy, purpura, and biopsy-proven vasculitis. In contrast, patients without ANCA have more frequent cardiac and pulmonary involvement (and fever), suggesting an eosinophilic tissue disease phenotype, and conceivably representing a variant of the HES with systemic manifestations [61]. 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 ANCA-negative EGPA phenotype.

Table 15.6 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 Peripheral neuropathy Purpura	Cardiac involvement (eosinophilic myocarditis) Fever
Predominant histopathologic features	Biopsy-proven vasculitis	Eosinophilic pneumonia

Adapted from Refs. [60, 61]
ANCA antineutrophil cytoplasmic antibody, *MPO* myeloperoxidase, *p-ANCA* perinuclear antineutrophil cytoplasmic antibody

Treatment and Prognosis

Treatment of EGPA is based on corticosteroids, which suffice in a large number of cases [45, 75–77]. 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 despite corticosteroids or after treatment has been discontinued, and may consist in relapses of the systemic vasculitis (usually accompanied by increased peripheral blood eosinophilia greater than 1×10^9), or more frequently in remitting or persistent difficult asthma that may require long-term low-dose oral corticosteroids despite optimal inhaled asthma therapy.

Patients with poor prognostic factors at onset that could result in mortality or severe morbidity should receive intravenous pulses of cyclophosphamide therapy (better tolerated than oral cyclophosphamide administration) in addition to corticosteroids. 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 EGPA ("revisited five factor score") [78]. Immunosuppressive therapy with cyclophosphamide is therefore warranted in patients with a five factor score >1 and especially those with heart failure [79, 80]. Cardiomyopathy is indeed the main predictor of mortality [74], especially in case of heart failure [79]. Disease control is improved by combination of immunosuppressors with corticosteroids, with the caveat of a higher risk of infections.

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 [74] and lower in those with baseline eosinophils $>3.0 \times 10^9$/L [80]. Although 12 cyclophosphamide pulses are better able to control the disease, a 6-pulses regimen is generally preferred when complete remission of the vasculitis is obtained, followed by maintenance therapy with oral azathioprine (or weekly intramuscular methotrexate) in addition to corticosteroids.

In recent series, almost 80 % of patients were alive at 5 years [49, 74, 75], and 97 % were alive at 5 years in EGPA without poor-prognosis factors [81]. Mortality is associated with disease severity. Most deaths during the first year of treatment are due to cardiac involvement [82]. Long-term morbidity is related to side effects of oral corticosteroids [81], and to frequent uncontrolled asthma with airflow obstruction (that may still be partly reversible with increased oral corticosteroid treatment [83]) despite corticosteroids and inhaled therapy [83, 84].

Some selected cases of severe EGPA refractory to corticosteroids and/or cyclophosphamide may benefit from subcutaneous interferon-alfa, high-dose intravenous immunoglobulins, cyclosporin A, or rituximab, however with low-level of evidence. In addition, the anti-IgE omalizumab has been used successfully to treat persistent asthma in patients with EGPA; careful clinical monitoring is warranted, because omalizumab does not control the systemic disease. Mepolizumab is under evaluation.

Hypereosinophilic Syndrome

The "idiopathic" HES was historically defined in 1975 by Chusid and coworkers [85] 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. As a treatment is often considered before irreversible systemic complications occur, the diagnosis of HES is now considered in patients with blood hypereosinophilia (greater than 1.5×10^9/L) on at least two occasions in the absence of other etiologies for the eosinophilia, allowing earlier diagnosis and management.

Pathogenesis

HES may result from a 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 as a premalignant T-cell disorder [86, 87] or a chronic leukemia, respectively. The term *idiopathic* is now restricted to 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 "lymphocytic variant" of HES (about 30 % of patients with HES), chemokines (especially IL-5) 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. 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 on 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.

In the chronic eosinophilic leukaemia ("myeloproliferative variant" of HES) (about 20–30 % of cases), 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, thrombocytemia, 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 [88, 89], 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.

Clinical and Imaging Features

The pulmonary involvement in patients with eosinophilia of clonal origin has not been studied specifically in the two variants of the HES, and most data available derive from older studies. Lung or pleural involvement is uncommon in the lymphocytic variant of the HES [86, 87]. However, pulmonary involvement is present at chest CT in about 40 % of patients with chronic eosinophilic leukemia [85, 90].

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 [90]. The mean eosinophil count at presentation was 20.1×10^9/L in one series [91], with occasionally extremely high values in excess of 100×10^9/L [85].

Patients present with weakness and fatigue (26 %), cough (24 %), dyspnea (16 %) [90], or asthmatic symptoms (25 %) [92]. Morbidity and mortality in HES are driven by cardiovascular involvement, with characteristic endomyocardial fibrosis [90] (which differs from the eosinophilic myocarditis seen in EGPA), causing dyspnea, congestive heart failure, mitral regurgitation, cardiomegaly [90], and typical features at echocardiography [93]. The other manifestations of HES include neurologic manifestations (thromboemboli, central nervous system dysfunction, and peripheral neuropathies), cutaneous manifestations (erythematous pruritic papules and nodules, urticaria, and angioedema).

Pulmonary involvement [85, 90] may manifest as pleural effusion, pulmonary emboli, interstitial opacities at imaging, or especially cough, which can be the predominant feature, be associated with bronchospasm, and be severe, with possibly frequent coughing attacks [91] . CT findings vary and are poorly specific [18], but most commonly consist of patchy ground-glass opacities and consolidation [92]. Small nodules, focal and peripheral areas of ground-glass attenuation, and occasionally a halo of ground-glass attenuation, may be observed. Notably, imaging features corresponding to eosinophilic lung involvement must be differentiated from those related to pulmonary edema resulting from cardiac involvement.

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 chronic eosinophilic leukemia, imatinib is the first-line therapy, with more frequent response when the Fip1L1 – PDGFR-α fusion protein is present [88, 89, 94]. 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 [95]. In patients with the "lymphocytic variant" of HES, corticosteroids remain the mainstay of treatment, although a response is obtained in only about half of them. 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 [96, 97]. Chemotherapeutic agents (hydroxyurea, vincristine, etoposide), cyclosporin A, and interferon-α either as monotherapy or in association with hydroxyurea, may be beneficial particularly in the myeloproliferative variant.

The long-term prognosis of HES has improved considerably, with a 3-year survival of only 12 % in the first published series [85], to about 80 % survival at 5 years and 50–70 % survival at 10 years in later series [90, 91]. 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.

Table 15.7 Working diagnostic criteria for hypereosinophilic obliterative bronchiolitis [98]

Peripheral blood and/or BAL	Blood eosinophil cell count $>1 \times 10^9$/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

All three criteria are required. Hypereosinophilic obliterative bronchiolitis may be secondary to various conditions including EGPA, ABPA, or drug-induced eosinophilic lung disease

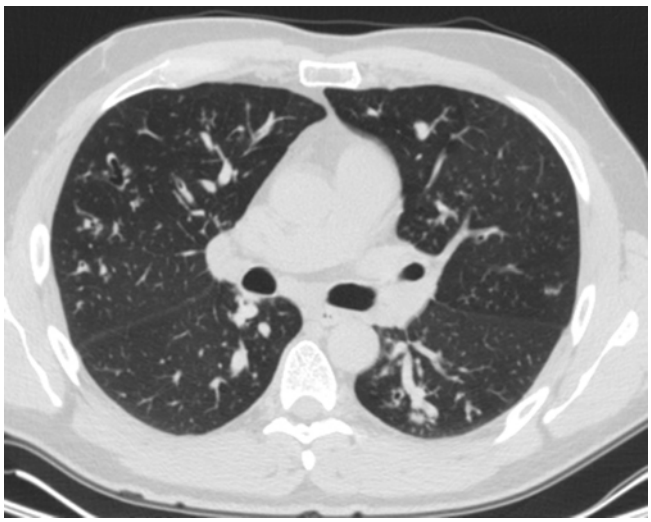

Fig. 15.7 CT scan of a patient with idiopathic hypereosinophilic bronchiolitis showing bronchiectasis in the right middle lobe and mucoid impaction in the left lower lobe

Idiopathic Hypereosinophilic Obliterative Bronchiolitis

Hypereosinophilic obliterative bronchiolitis is a recently individualized entity [98], currently defined by provisional working criteria (Table 15.7), associating demonstration of bronchiolitis, of peripheral blood and/or alveolar eosinophilia, and persistent airflow obstruction despite high-dose inhaled bronchodilators and corticosteroids. Demonstration of a bronchiolitis may be obtained by lung biopsy [98–100] and/or HRCT showing direct signs of bronchiolitis (e.g. centrilobular nodules and branching opacities) [98] (Fig. 15.7). 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 [98].

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 [98]. Airflow obstruction is often severe but reversible in all cases with 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. Unrecognised 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 at bronchial biopsy [98].

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 [101].

Eosinophilic Pneumonias of Parasitic Origin [101, 102]

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 [103]

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, high blood eosinophilia, and disseminated bilateral opacities at 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 3,300 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's 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, 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 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 [104]. Only symptomatic treatment is generally required. The use of antihelmintics 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. Löffler's 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 in 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's 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 brasiliense*. 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's-like pneumonitis) may develop in chronic schistosomiasis (in addition to the risk of portopulmonary hypertension) [105]. 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 % [106, 107] 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), however not reflecting the natural course of disease in many patients, and alternative staging systems have been proposed [108]. Allergic *Aspergillus* sinusitis, a sinus equivalent of ABPA [109], can be associated with ABPA in a syndrome called *sinobronchial allergic aspergillosis.*

Pathogenesis

ABPA results from damage to the bronchial epithelium, submucosa, and adjacent pulmonary parenchyma caused by a chronic inflammatory reaction in the bronchi and the surrounding parenchyma. It 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 [110] to antigens from *Aspergillus* growing in mucous plugs in the airways. In addition to mechanisms associated with innate and acquired immunity, ABPA can occur preferentially in genetically susceptible hosts, as suggested by increased prevalence of heterozygotic cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations [111, 112], and association with a polymorphism within the IL-4 receptor α-chain gene and HLA DR subtypes. Infection with nontuberculous mycobacteria [113], infliximab therapy for sarcoidosis [114], and occupational exposures (in workers in the bagasse-containing sites in sugar cane mills) [115] 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 [116]), with difficulties in assessing the sensitization to the specific fungi probably accounting for part of the low frequency of this condition as compared to ABPA.

Diagnostic Criteria

Revised criteria, which still need validation, have recently been proposed recently (Table 15.8) [108]. 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,

Table 15.8 Diagnostic criteria of ABPA

Minimal essential diagnostic criteria of ABPA [119]	
Patients with asthma and central bronchiectasis	1. Asthma 2. Central bronchiectasis (inner 2/3 of chest CT field) 3. Immediate cutaneous reactivity to *Aspergillus* 4. Total serum IgE concentration >417 kU/L (1,000 mg/mL) 5. Elevated serum IgE-*A. fumigatus* and/or IgG-*A. fumigatus* (infiltrates on chest radiograph and serum precipitating antibodies to *A. fumigatus* may be present but are not minimal essential diagnostic criteria)
Patients with asthma (ABPA –seropositive)	Patients with the above criteria 1, 3, 4, 5 (infiltrates on chest radiograph may be present but are not a minimal essential diagnostic criteria)
Patients with cystic fibrosis	Clinical deterioration (increased cough, wheezing, exercise intolerance, increase sputum, decrease in pulmonary function) Immediate cutaneous reactivity to *Aspergillus* or presence of IgE-*A. fumigatus* Total serum IgE concentration ≥1,000 kU/L Precipitating antibodies to *A. fumigatus* or serum IgG-*A. fumigatus* Abnormal chest radiograph (infiltrates, mucus plugging, or a change from earlier films)
Newly proposed diagnostic criteria [108]	
Predisposing conditions	Bronchial asthma Cystic fibrosis
Obligatory criteria (both should be present)	Type I *Aspergillus* skin test positive (immediate cutaneous hypersensitivity to *Aspergillus* antigen) or elevated IgE levels against *Aspergillus fumigatus* Elevated total IgE levels (>1,000 IU/mL)[a]
Other criteria (at least two of three)	Presence of precipitating or IgG antibodies against *A. fumigatus* in serum Radiographic pulmonary opacities consistent with ABPA[b] Total eosinophil count >500 cellsL in steroid naive patients (may be historical)

[a]If the patient meets all other criteria, an IgE value <1,000 IU/mL may be acceptable

[b]The chest radiographic features consistent with ABPA may be transient (i.e. consolidation, nodules, tram-track opacities, toothpaste/finger-in-glove opacities, fleeting opacities) or permanent (i.e. parallel line and ring shadows, bronchiectasis and pleuropulmonary fibrosis)

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* [117, 118]). The expectoration of mucous plugs, the presence of *Aspergillus* in sputum, and late skin reactivity to *Aspergillus* antigen [117] are also frequent findings that contribute to the diagnosis when present. Typical proximal bronchiectasis may be absent in cases designated ABPA-seropositive [119]. 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 [108]. 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 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, out of which 22 are available as recombinant allergens (named *Asp f1* to *Asp f22*) [119], two seem to be the most helpful for diagnostic purposes (e.g. specific antibodies to recombinant *Asp f4* and *Asp f6*) [120].

Imaging

Proximal bronchiectasis on CT (in the medial half of the lung from the hilum to the chest wall) predominating in the upper lobes [121] are considered a hallmark of ABPA, although they lack both sensitivity and specificity, and may be absent especially in early disease [108], although it has been suggested that serological ABPA (without bronchiectasis) may correspond to a variant rather than an early stage of disease [122]. Bronchiectasis represent the ultimate consequence of damage to the large bronchi by chronic inflammation. Mucoid impaction of high attenuation on CT represent mucous plugs containing *Aspergillus* obstructing the airways with subsequent atelectasis. Mosaic attenuation, centrilobular nodules, and tree-in-bud opacities are also commonly seen. The presence of bronchiectasis, centrilobular nodules, and mucoid impaction on CT scan are highly suggestive of ABPA in an asthmatic (Figs. 15.8, 15.9 and 15.10) [123]. Agarwal et al. have suggested a classification based on CT imaging pattern between serological ABPA (without bronchiectasis), ABPA with bronchiectasis, ABPA with high-attenuation mucus, and ABPA with pleuropulmonary fibrosis [108].

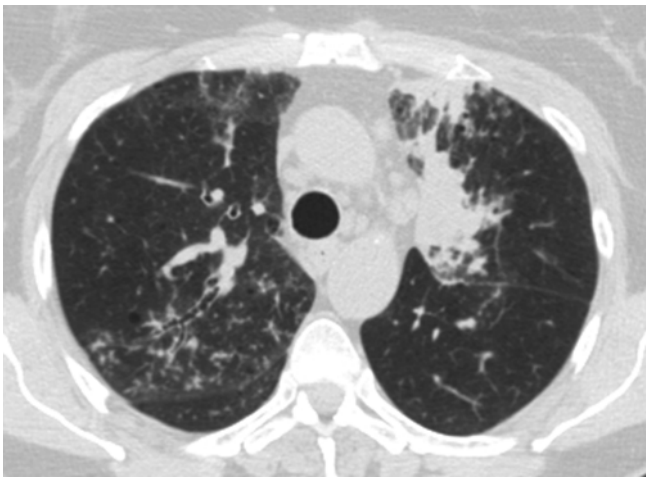

Fig. 15.8 CT scan of a patient with allergic bronchopulmonary aspergillosis showing central bronchiectasis and tree-in-bud pattern in the right upper lobe, with alveolar consolidation corresponding to eosinophilic pneumonia in the left upper lobe

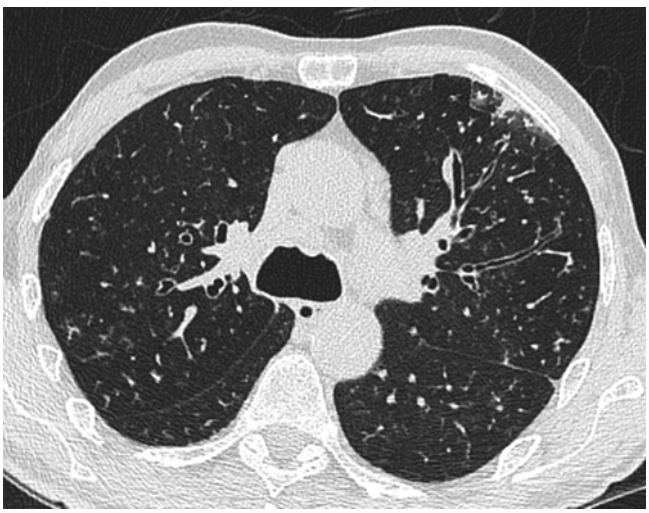

Fig. 15.9 CT scan of a patient with allergic bronchopulmonary aspergillosis showing central bronchiectasis predominating in the left upper lobe, with mild subpleural alveolar consolidation

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 to atelectasis.

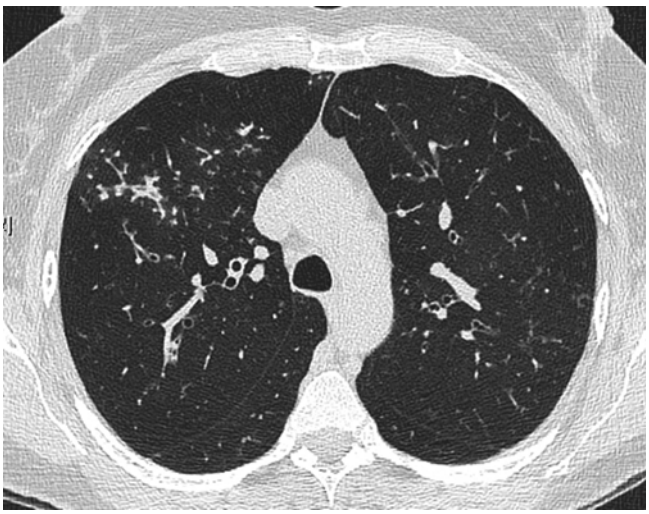

Fig. 15.10 CT scan of a patient with allergic bronchopulmonary aspergillosis showing peripheral tree-in-bud and branching pattern in the right upper lobe

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. Oral corticosteroids are maintained on 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, although with low-level evidence. In two double-blind, randomized, placebo-controlled studies [124, 125], oral itraconazole allowed reduction of the doses of corticosteroids, decrease in the number of exacerbations [125], and improvement of biologic (sputum eosinophils, sputum ECP levels, serum IgE levels, and serum IgG levels to *A. fumigatus*) and physiologic criteria, suggesting a clinical benefit in approximatively 60 % of patients with ABPA [126], especially those with corticosteroid-dependent ABPA; no significant effect was observed on pulmonary infiltrates [127]. Itraconazole is therefore recommended in ABPA in asthmatics [128]. It may also be useful in ABPA patients with cystic fibrosis [126, 129]. Itraconazole therapy is generally continued for a minimum of 4–6 months. Monitoring total serum IgE level may be helpful, with an objective of reducing the serum total IgE level by ≥25 % with therapy [108]. 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 [126].

In spite of total IgE levels that frequently exceed 1,000 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 [130, 131]. In isolated difficult cases, some clinical benefit was suggested with pulses of intravenous corticosteroids (to treat exacerbations), voriconazole, posaconazole, or nebulised liposomal amphotericin B.

Bronchocentric Granulomatosis

Bronchocentric granulomatosis [132] is a chronic inflammatory granulomatous and destructive process extending from the bronchiolar walls into the surrounding peribronchiolar lung parenchyma [133]. 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 [133]. In asthmatics, eosinophils are prominent within the inflammatory infiltrate of bronchocentric granulomatosis, whereas they are less conspicuous in non asthmatics. Patients with bronchocentric granulomatosis often present clinically as asthmatics who have fever, chronic cough, and peripheral blood eosinophilia greater than 1×10^9 eosinophils/L [133]. Imaging features consist of masses, alveolar opacities, or consolidation, and possible reticulonodular opacities. Abnormalities all predominate in the upper lung zones and are generally unilateral [134]. Management is based on oral corticosteroids. As most of these patients also fulfill the criteria for ABPA, this condition may be underdiagnosed. However, prognosis is excellent, with common recurrences.

Drug, Toxic Agents, and Radiation-Induced Eosinophilic Pneumonias

Eosinophilic pulmonary infiltrates can be caused by a number of drugs (Table 15.9, see www.pneumotox.com), with 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's 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. Pleural effusion is possible. Systemic eosinophilic vasculitis involving the lung and closely resembling EGPA has been reported. Cases with

Table 15.9 Drugs that may commonly cause acute eosinophilic pneumonia

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, trimetoprime-sulfamethoxazole
Other drugs	Captopril, carbamazepine, Granulocyte Monocyte-Colony Stimulating Factor (GM-CSF)

A more extensive list of drugs reported to cause eosinophilic pneumonia may be found at www.pneumotox.com

severe pulmonary involvement may require mechanical ventilation, or present with systemic manifestations (drug reaction with eosinophilia and systemic symptoms, DRESS) [135, 136].

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). 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 be considered in rare occasions.

The toxic oil syndrome and the eosinophilia-myalgia syndrome related to preparations of L-tryptophan are historical causes of toxic-induced eosiphilic lung disease that occurred in Spain in 1981 and in the United States in 1989, respectively.

A syndrome similar to ICEP can develop up to 10 months after radiotherapy for breast cancer in women. 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.

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 usually moderate eosinophilia in BAL in organizing pneumonia, with foci of organizing pneumonia in ICEP or conspicuous eosinophils in organizing pneumonia at pathology, or evolution of untreated CEP to organizing pneumonia.

Eosinophilic inflammation of the airways is frequent in asthma, plays a role in disease pathogeny [137], and correlates with the severity of disease [138]. 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 numbers, is a marker of steroid-responsive disease, with a high risk of exacerbations, and may respond to anti-IL5 monoclonal antibodies [139]. Patients with asthma and high-level blood hypereosinophilia (i.e., >1.0 and especially $>1.5.10^{-9}$) or alveolar eosinophilia (>25 % and especially >40 %), considered to have "hypereosinophilic asthma" [140, 141], 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 sputum with normal lung function and absence of bronchial hyperreactivity [142]; eosinophilic bronchitis is clearly distinct from asthma and from hypereosinophilic obliterative bronchiolitis, however it can cause chronic cough responsive to inhaled corticosteroid treatment [143], and rarely may evolve to irreversible airflow obstruction [144, 145]. Treatment with an antagonist of the eotaxin tissue receptor CCR3, the receptor for eotaxin and other chemokines, may be beneficial [146]. Eosinophilic bronchitis is distinct from bronchial asthma.

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 [147], or may result from infection.

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Multiple Cystic Lung Diseases

16

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Abbreviations

AIDS	Acquired immunodeficiency syndrome
BALT	Bronchus-associated lymphoid tissue
CCAM	Congenital cystic adenomatoid malformation
CPAM	Congenital pulmonary airway malformation
CT	Computed tomography
FLCN-S	Folliculin (*FLCN*) gene-associated syndrome (Birt-Hogg-Dubé)
HRCT	High resolution computed tomography
LAM	Lymphangioleiomyomatosis
LIP	Lymphoid interstitial pneumonia
MCLD	Multiple cystic lung disease
PLCH	Pulmonary Langerhans' cell histiocytosis (formerly histiocytosis X)
RRP	Recurrent respiratory papillomatosis
SS	Sjögren syndrome
TSC	Tuberous sclerosis complex

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Cysts and Other Lucencies

Cysts

A pulmonary *cyst* [1] is defined as "a round parenchymal lucency of low-attenuation area with a well-defined interface with normal lung" [2]. The thickness of the cyst wall is less than 2 mm. It contains air however fluid or solid material may be present. Some cysts of unknown cause may be present in up to 25 % of people over 75 years of age [3].

The term of cyst is often used to describe enlarged thin-walled airspaces especially in patients with lymphangioleiomyomatosis (LAM) or pulmonary Langerhans cell histiocytosis (PLCH); thicker-walled honeycomb cysts are seen in patients with end-stage fibrosis.

Cysts may be the only type of lesion seen on HRCT imaging, however depending on the aetiology other types of associated lesions may be present such as nodules (especially cavitary) in Langerhans cell histiocytosis (LCH) or diffuse ground glass opacities in lymphoid interstitial pneumonia (LIP).

Other Lucencies

A *cavity* is a "gas-filled space, seen as a lucency or low-attenuation area, within pulmonary consolidation, a mass, or a nodule. It is usually produced by the expulsion or drainage of a necrotic part of the lesion via the bronchial tree. It sometimes contains a fluid level" [2].

A *bulla* is a "rounded focal lucency or area of decreased attenuation, 1 cm or more in diameter, bounded by a thin wall. Multiple bullae are often associated with other signs of pulmonary emphysema (centri-lobular and paraseptal)" [2].

A *pneumatocele* is "an approximately round thin-walled airspace in the lung most frequently caused by acute pneumonia, trauma, or aspiration of hydrocarbon fluid" [2].

Varicose and cystic bronchiectasis especially in the upper lobes may mimick as multiple, thick-walled, irregular cysts however they are connected to the bronchial tree.

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Multiple Cystic Lung Disease (MCLD): The "Big Three"

The "big three" MCLD are rare but not exceptional conditions which comprise lymphangioleiomyomatosis (LAM), sporadic or associated with tuberous sclerosis (TSC), Langerhans cell histiocytosis (LCH), and the *FLCN* syndrome (Birt-Hogg-Dubé). Since LAM and LCH are developed in specific chapters of this book, we shall especially focus on the latter.

The initial clinical pulmonary manifestations of the big three are dominated by the occurrence of spontaneous pneumothorax often relapsing. The progressive destruction of the lung with the multiplication and increase in size of the pulmonary cysts may lead to respiratory failure.

The other miscellaneous causes of MCLD are listed in Table 16.1.

FLCN Gene-Associated Syndrome (Birt-Hogg-Dubé)

History of Cutaneous, Pulmonary, and Renal Manifestations

Cutaneous Manifestations

Perifollicular fibromas (about 100) which had appeared 6 years earlier on the neck and the nape of the neck were reported in 1925 by R. Burnier and J. Rejsek in a 56 year old woman [4]. Multiple perifollicular fibromas of the face and neck which had appeared in a 53 year old man by the age of 32 years, the brother and a cousin of whom had the same dermatosis (at a lesser degree) were later reported by J. Civatte and J.P. Le Tréguilly [5]. A.R. Birt, G.R. Hogg, and J. Dubé reported in 1977 multiple fibrofolliculomas in a family with hereditary medullary carcinoma of the thyroid, a condition now recognized as a tumour suppressor gene syndrome caused by a germline *RET* mutation [6]. Thirty-seven members of the kindred of 70 were more than 25 years of age, and 15 of them had fibrofolliculomas (confirmed by biopsy in ten lesions taken from six patients). Trichodiscomas and acrochordons were also present.

Pulmonary Manifestations (Pneumothorax, Lung Cysts)

It is an unusual event which revealed the probable first reported case of the syndrome with pulmonary manifestations in 1960 [7]. JRW, a 20 year-old man, was taught for submarine escape training at US Submarine Escape Training tanks. The technique for escape was as follows. The person escaping enters a special isolated compartment, which is then flooded from the sea to about chest level. With compressed air the pressure within the compartment is increased to equal the outside sea pressure. The escape hatch can then be opened, allowing access to the sea. With an inflated Mae West life

Table 16.1 Causes of Pulmonary MCLD

Folliculin gene (*FLCN*)-associated syndrome
Birt-Hogg-Dubé syndrome
Familial spontaneous pneumothorax
Lymphangioleiomyomatosis
Sporadic
Tuberous sclerosis complex associated
Pulmonary Langerhans cell histiocytosis
Lymphoid disorders
Lymphoid interstitial pneumonia, idiopathic or associated with connective tissue disease (especially Sjögren syndrome)
Pulmonary lymphoma
Amyloidosis
Non-amyloid immunoglobulin deposition disease
Infections
Staphylococcal and other bacterial causes
Pneumocystis jiroveci infection in AIDS and nonAIDS immunocompromised patients
Recurrent respiratory papillomatosis
Hyper-IgE syndrome
Tumours
Metastases of sarcoma
Metastases of benign uterine leiomyoma
Metastases of other tumours
Congenital cystic disorders
Other causes
Genetic disorders (neurofibromatosis, Ehlers-Danlos syndrome, Proteus syndrome, others)
Interstitial lung diseases (hypersensitivity pneumonias, desquamative interstitial pneumonia)
Others (posttraumatic pseudocysts, Erdheim-Chester disease, fire-eater's lung, etc.)

jacket the man escaping then steps into the sea and rises to the surface at a rate of about 375 ft per minute. The compressed air within the life jacket is vented through special valves to prevent rupture of the jacket through expansion of its contained air as the surface is approached. The man escaping exhales continually during his ascent.

JRW had a normal chest X-ray. He followed the procedure and left the area. He was found lying on the grass in a stuporous condition 30 mn later, then improved. He did two consecutive other procedures and collapsed after the second. Recompression was done, resulting in improvement, then decompression could be done.

Chest X-ray showed several cystic areas in the left upper lobe, some of which with air levels. It was supposed that this was a case of air embolism associated with acute development of pulmonary cysts during decompression from depth.

Over the 50 following years JRW was admitted five times at hospital for pneumothorax. He further had a curative resection for clear cell-type renal carcinoma. An (astute) intern at hospital eventually considered the possibility of the syndrome. The patient had indeed removal of acrochordons several times. He further had a colorectal adenoma [8].

"Unilateral lung cysts" (not otherwise precised) were reported in 1975 by Hornstein and Knickenberg [9] in a man with further kidney cysts and solid nodules on his face, neck, and back. His daughter had innumerable perifollicular fibromas on the face, neck and trunk, a large goitre, and adenomatous colon polyps one of them transformed into carcinoma.

Perifollicular fibromas were further reported in 1986 in a man with colon polyposis who developed iterative spontaneous pneumothoraces. Spontaneous pneumothorax had occurred in seven people in the family, including four with perifollicular fibromas with further colon polyposis [10].

Chung et al. [11] later reported multiple spontaneous pneumothoraces starting at 15 years of age with bullous emphysema in his early twenties in a male patient with skin fibrofolliculomas.

Toro et al. [12] reported pulmonary cysts present in 4 of 28 patients from kindreds with familial renal tumors. Of these patients 3 had characteristic skin features, and one developed pneumothorax.

Renal Tumours

Bilateral chromophobe renal adenocarcinoma was reported in 1993 by Roth et al. [13] in a patient with characteristic fibrofolliculomas on the face, neck, and upper chest.

Toro et al. [12] in a study of kindreds with familial renal cancer found 13 patients with the syndrome. Of these 3 had lung cysts.

Towards a Novel Non-eponymous Terminology of the Syndrome

The above review clearly demonstrates that A.R. Birt, G.R. Hogg, and W.J. Dubé [6] were not the first to describe familial multiple skin fibrofolliculomas. They further did not describe the other cardinal features of the condition i.e. MCLD and renal cancer.

It has been suggested that the name of Hornstein is added to those of the above authors [14] because he reported multiple perifollicular fibromas, polyps of the colon, and unilateral lung cysts. Further Furaya and Nakatoni [15] suggested to rename the syndrome as the name of the woman physician who worked with Hornstein was omitted. Thus the eponymous name of the condition would become at least Hornstein-Knickenberg-Birt-Hogg-Dubé syndrome, a bizarre terminology.

Because eponyms do not always correspond to the first and/or principal contributors to the genuine entity, we further agree that a descriptive anonymous terminology is more appropriate [16].

We have proposed at the Fifth Birt-Hogg-Dubé symposium 2013 in Paris that the condition be called *FLCN* (folliculin) gene-associated syndrome (in short *FLCN* syndrome, or *FLCN*-S).

A definite diagnosis should ideally rely on the finding of a mutation in the *FLCN* gene and the presence of MCLD and/or multiple characteristic skin lesions and/or malignant kidney tumour. However although some diagnostic criteria have been proposed [17, 18] no consensus between geneticists, dermatologists, pulmonologists, and oncologists has hitherto been established.

Clinical Features

Pulmonary Manifestations

Pneumothorax is a characteristic feature [19–29] which has been reported as early as at age 7 years in the son of a patient [30]. In contrast patients may not develop pneumothorax throughout their lifetime as in a 85-year-old man with characteristic skin features present since young adulthood who had multiple pulmonary cysts detected by HRCT only once the diagnosis of *FLCN*-S was established in his son [31].

In a large series [22] of 98 patients affected with the *FLCN*-S, 13 carriers of *FLCN* haplotype, and 112 unaffected family members, the age-adjusted odds-ratio for pneumothorax in *FLCN*-S individuals was 50.3 times higher. In a larger cohort of 198 patients from the same institution, all 48 patients with a history of pneumothorax had multiple lung cysts identified by chest CT imaging [23]. The median age of occurrence of the first pneumothorax was 38 years (with a range from 22 to 71 years). Seventy five percent of patients had a second pneumothorax. There was no association between smoking and the risk of pneumothorax. Exon location of the *BHD* mutation was associated with the number of cysts, with individuals with mutations in exon 9 having more cysts. In a further study [24] of 51 families with *FLCN*-S, 88 % of the families and 84 % of the patients had lung cysts on CT imaging.

Fifty-three percent of families and 38 % of individuals had a history of spontaneous pneumothorax. Most patients with a history of pneumothorax had lung cysts by CT imaging. Fifty-eight percent of patients with a family history of pneumothorax developed pneumothorax compared to 28 % without a family history ($p = 0.01$). A family history of pneumothorax was not associated with an increased risk of kidney tumours. Out of 34 individuals with a total of 92 spontaneous pneumothoraces, 19 had 2 pneumothoraces, and 7 had 3–7 pneumothoraces.

Interestingly, pneumothoraces without cysts on CT imaging have been reported [19]. A pneumothorax was reported in a 33 year-old-woman after a long airplane flight, leading to the diagnosis of MCLD and further *FLCN*-S [32]. Pneumomediastinum developed in a patient with *FLCN* mutation, without skin or renal manifestations, with pneumothoraces with or without detected lung cysts in four of family members [33].

Imaging

In a series of 17 patients with *FLCN*-S established by genetic testing [34], MCLD was present in 15 cases (bilateral in 13, and unilateral in 2). The distribution of the cysts predominated in the lower part of the lungs (13/15). Five patients had more than 20 cysts and 7 fewer than 10 cysts, the size of which ranged from 0.2 to 7.8 cm. The shape of the cysts varied from round to oval with the large cysts usually having a lobulated multiseptal appearance. In another study of 12 patients [35] the number of cysts varied from 29 to 407, with 77 % of cysts being of irregular shape, and 40 % located along the pleura. Distribution of cysts predominated in the lower medial zone (i.e. below the level of the tracheal carina, and in the inner half of the lung field). Cysts abutting or including the proximal portions of lower arteries or veins were present in all patients. The same group further compared the pulmonary cysts in patients with *FLCN*-S and in patients with LAM [36]. Females with *FLCN*-S were older (46 vs 36 year old), with a prevalence of 6/14 with a family history of pneumothorax within the second degree relatives (vs none in LAM patients). The percentage of the ratio of pulmonary cysts' areas in each lung field, the number of cysts and the mean circularity of cysts (roundness) was greater in LAM; the mean size of cysts was greater in *FLCN*-S. The number and size of cysts in the reported studies is quite variable: some patients had only few cysts (5 or less to 10) whereas they were innumerable in other patients, with a size varying from a few millimetres up to 10 cm (Fig. 16.1).

Exon location of the *FLCN* mutation is associated with the number of cysts, with individuals with mutation in exon 9 having more cysts than individuals with mutation in other exons.

Pathology

Resected lung specimens of *FLCN*-S have often been diagnosed by pathologists as nonspecific blebs or bullae or emphysema [15]. The pathologic features mentioned in case reports usually did not identify specific lesions, however most often only specimen of subpleural lung tissue were taken at the time of pleurodesis after pneumothorax, with wedge lung biopsy further obtained in only a few cases. These reports mentioned possible associated inflammation attributed to chronic pneumothorax.

Histopathological study of two cases with basilar cysts found intraparenchymal collections of air surrounded by normal parenchyma or a thin fibrous wall, and blebs (consisting of collection of air within the pleura). Although these features were not specific to *FLCN*-S their predominantly basal location contrasted with the apical distribution of the other more common causes of spontaneous pneumothorax especially emphysematous bullae or idiopathic blebs [37]. The cysts in *FLCN*-S are typically punch out intraparenchymal cysts without inflammation [38]. A detailed analysis [39] was done on three wedge-resected tissues containing several cysts up to 1 cm in diameter, mostly in the pleural and subpleural regions. On microscopy these were found to be located in the vicinity of the interlobular septa, visceral pleura, and junctional regions between the interlobular septum and visceral pleura. Each cyst was incorporated with interstitial stroma of the interlobular septum and/or pleural in part, and with normal alveolar structures in the other part. Some cysts had protrusion of veins into the cystic space, a feature of an intimate spatial relationship of blood vessels and pulmonary cysts [28, 39, 40]. It was proposed that the pulmonary cysts in *FLCN*-S may represent an aberrant cystic alveolar formation with deranged interaction between alveolar epithelial structures and the surrounding mesenchyma in the peripheral lobular compartment that may give rise to the formation of abnormal cysts without stromal reaction. Pneumothorax might result from further growth of cysts [39]. Histopathological and morphometric analysis of 229 pulmonary cysts from 50 unrelated *FLCN*-S and 117 cysts from 34 patients with primary spontaneous pneumothorax were compared [41]. *FLCN*-S cysts differed significantly from primary spontaneous pneumothorax cysts by abutting on interlobular septa (88 %), having intracystic septa (14 %) or protruding venules (39 %) without cell proliferation or inflammation. Although the intrapulmonary *FLCN*-S cysts were smaller than the subpleural ones there was no difference in size between them when there was no inflammation. The conclusion of this study was that *FLCN*-S cysts are likely to develop in the periacinar region, an anatomically weak site in a primary lobule, where alveoli attach to connective tissue septa. The authors hypothesized that the *FLCN*-S cysts possibly expend in size as the alveolar walls disappear at the alveolar-septal junction, and grow even larger when

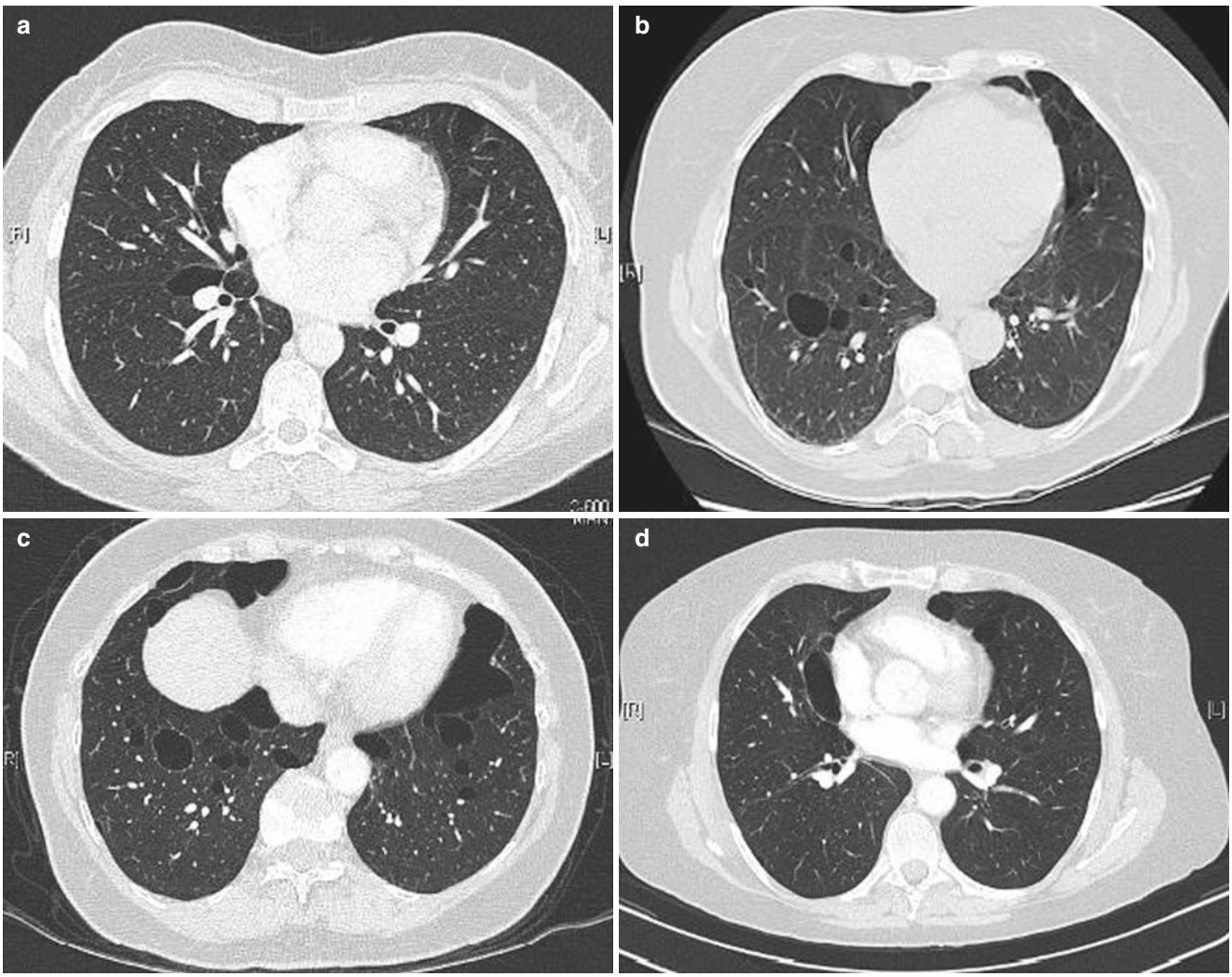

Fig. 16.1 Cysts in *FLCN*-syndrome. (**a**) Cyst of the lower medial zone, abutting the proximal portion of pulmonary vessels, oval shaped. (**b**) Cysts of the lower medial zone, round shaped. (**c**) Round, oval, and irregular shaped cysts. (**d**) Oval cyst bordering the pleura (*left*) and intraparenchymal cysts (which border the pleura)

several cysts merge. A study of eight cases reported that pulmonary cysts have their inner surface lined by epithelial cells, sometimes with a predominance of type II pneumocyte-like cuboidal cells with the cells constituting the cysts staining positive for phospho-S6 ribosomal protein expression, thus suggesting activation of the mTOR pathway [42]. Activation of the mTOR pathway has been considered in both TSC and *FLCN*-S. Facial hair follicle tumours (angiofibromas) in TSC patients coincidentally responded to the oral mTOR inhibitor rapamycin administrated after renal transplantation, and to topical rapamycin. However a topical rapamycin double-blind placebo-controlled randomised split-face trial did not demonstrate cosmetic improvement of fibrofolliculomas in *FLCN*-S patients [43]. Folliculin in the lung cysts studied by immunochemistry [39] was present in macrophages and epithelial cells in the lungs of the patients and normal control lungs. In the cyst lesions the pneumocytes that lined the inner surface of cysts were also immunostained for folliculin. Wedge biopsy in a patient with *FLCN*-S and a history of ten pack-years of smoking reported widespread emphysematous changes, with further an interlobular septum replaced by interstitial air resulting in the displacement and compression of the venous wall on the side abutting the air-filled space [25].

Cutaneous Manifestations

Characteristic multiple, dome-shaped, whitish papules usually develop after the age of 20 years, especially on the face (nose and cheeks). These are common on the neck, and they are sometimes present on the trunk or the ears. Histologically they consist of benign hair follicle tumours called fibrofolliculomas (Fig. 16.2).

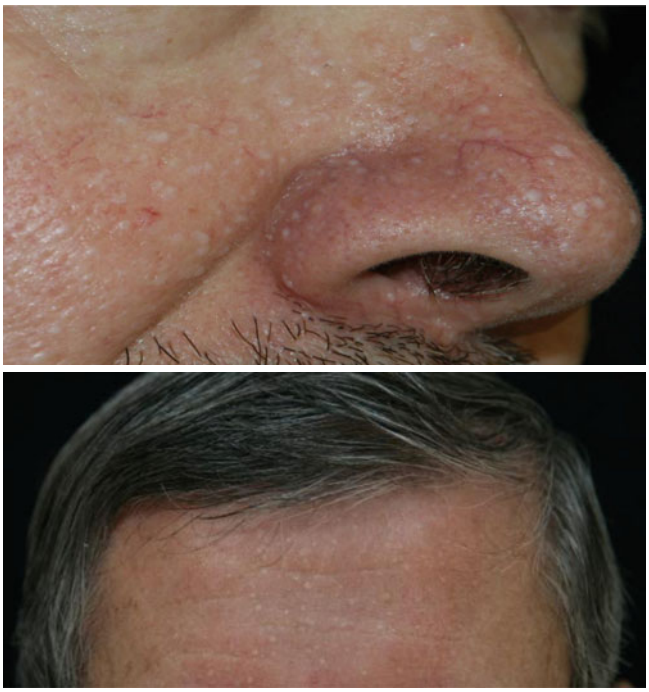

Fig. 16.2 Characteristic skin fibrofolliculomas in *FLCN*-S (Courtesy of D. Jullien, Lyon)

In their original description Birt et al. [6] described, in addition to fibrofolliculomas, trichodiscomas and acrochondromas. Whereas the first two belong to a morphological spectrum, acrochondromas are common in the general population. The diagnosis of the skin lesions relies on clinical examination by an experienced dermatologist with further histological examination if necessary.

Renal Manifestations

Renal cancer is the most threatening manifestation of the *FLCN*-S, occurring in up to one fourth of patients at a mean age of 50 years, and at a minimal age of 20. The most common histological types are chromophobe renal cancer, and a mixed pattern of chromophobe and oncocytic renal tumours. Renal cancer is multifocal and/or bilateral in more than half of patients with *FLCN*-S.

Most of these tumours are in the low-risk oncocytic renal neoplasia spectrum including chromophobe renal cell carcinoma, oncocytoma, and hydrid oncocytic tumours; clear cell and papillary renal cell carcinoma have also been reported [44, 45].

Renal (small size) angiomyolipoma [46] and renal cysts [12] has been reported in *FLCN*-S. Surveillance for renal tumours by annual magnetic resonance imaging starting by the age of 20 may be proposed.

Surveillance for renal tumours by annual magnetic resonance imaging starting by the age of 20 may be proposed.

Other Manifestations

Parotidal Tumours

Parotid gland oncocytic tumours have been reported in patients with *FLCN*-S [47].

Colorectal Polyps and Carcinoma

Colorectal polyps and carcinomas have been reported in patients with *FLCN*-S [9, 26, 48]. However systematic colonoscopy in 45 patients did not show an increased prevalence of colorectal neoplasm [22]. An increased risk of colorectal cancer might apply only to specific subgroups of patients with *FLCN*-S [26].

It has been suggested that *FLCN* is involved in the tumourigenesis of a subset of microsatellite stable sporadic colorectal carcinomas, and that the allelic loss in the region close to *FLCN* may play a role in colorectal tumour progression [49].

Clinical Vignette

A non-smoker woman, born 1951, had a first right pneumothorax in 1994 treated by intercostal tube drainage.

A relapse of pneumothorax (1995) led to thoracoscopic surgical resection of bullous dystrophy of the apical segment of the right upper lobe (no specific features present at pathological examination).

The patient further experienced 5 right pneumothoraces before she underwent in 2002 a right thoracotomy showing several subpleural bullous lesions. Pleurectomy was done.

She was referred for evaluation at the expert centre in 2011. HRCT demonstrated several pulmonary cysts with a maximum diameter of 18 mm. Lung function tests showed normal spirometry, moderate decrease of DLCO (81 % predicted), and no oxygen desaturation on exercise.

Dermatologic examination disclosed only two small papulous skin not characteristic of fibrofolliculoma lesions on the left cheek-bone (of which the patient refused biopsy).

No tumour was present at renal magnetic resonance imaging.

Heterozygous deletion of exon 14 of the *FLCN* gene led to the diagnosis of *FLCN*-syndrome (Birt-Hogg-Dubé).

FLCN Gene-Associated Familial Spontaneous Pneumothorax

A series of patients (24 females and 6 males) with *FLCN* mutations with pneumothorax and/or MCLD as the presenting feature was reported from the main institution in Japan where patients with suspected or diagnosed LAM are most

often referred to [27]. Skin lesions of *FLCN*-S were present in only 7 and renal tumors in 2, and thus the majority of patients had neither skin nor renal involvement suggestive of *FLCN*-S. The same group further reported germline mutations of the *FLCN* gene in patients with multiple lung cysts and recurrent pneumothorax who had neither skin nor renal lesions [28].

A Chinese study reported patients with sporadic and familial isolated primary spontaneous pneumothorax with *FLCN* mutations [50]. Lung cysts were present but no other features were associated. *FLCN* deletion was reported in a large Finnish family with a dominantly inherited tendency to primary spontaneous pneumothorax [51]. All carriers of the deletion had between 1 and more than 30 cysts, 1–6 cm in diameter. The deletion was not present in unaffected family members or in control samples. As the Finnish family under investigation had only pulmonary manifestations, the absence of other *FLCN*-S symptoms could be due to the location of the deletion which occurred in the first coding exon (in contrast with almost all other mutations in *FLCN* which are truncations occurring downstream in the gene). A study of primary spontaneous pneumothorax in a Swiss family with *FLCN* mutation did not disclose other *FLCN*-S manifestations [52], as well as in another English family [53] where antenatal localised lobar cystic malformation was discovered in two patients (at 34 week gestation in one) which had no significant clinical consequences during life.

The above studies show that *FLCN*-S may manifest only with relapsing pneumothorax and MCLD, with occasionally minimal or no cutaneous manifestations.

Only limited information is available about the pulmonary functional consequences of *FLCN* -associated MCLD. With the exception of pneumothorax often relapsing, the pulmonary involvement is usually asymptomatic with lung function tests mostly normal or subnormal [25, 29]. No information on pulmonary prognosis is currently available.

Lymphangioleiomyomatosis

LAM is characterised by the proliferation of abnormal smooth muscle cells resulting in the formation of multiple lung cysts and further the possible development of chyle-filled cystic lesions in the axial lymphatics [54].

Sporadic LAM occurs almost exclusively in women, and in up to 40 % adult women with the genetic disease tuberous sclerosis complex. Sporadic and TSC-LAM are indistinguishable clinically and histologically, although in TSC-LAM multifocal micro nodular pneumocyte hyperplasia may also be present. Both TSC and LAM are associated with abnormalities in one of the two TSC genes (*TSC1* and *TSC2*), in sporadic LAM generally *TSC2* [55, 56].

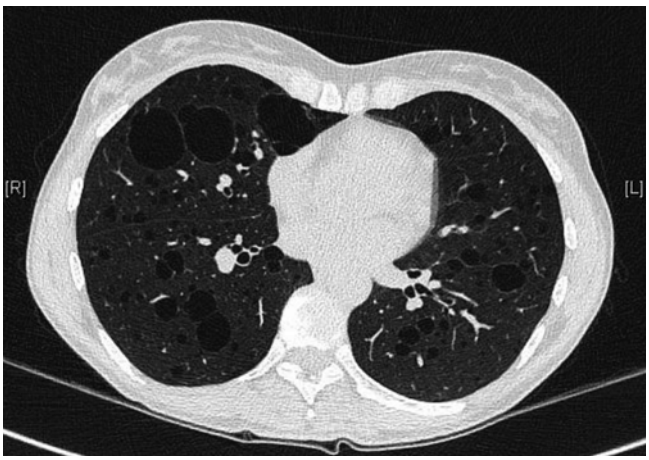

Fig. 16.3 Multiple cysts in LAM

Clinical Features

The first symptoms of LAM usually develop between 20 and 40 years of age however it may be recognised only after the menopause. Three-quarters of patients will experience pneumothorax and in about two-thirds of these it will be recurrent. Bilateral pneumothorax, pneumothorax during pregnancy, or recurrent pneumothorax in a young woman who does not smoke is suggestive of LAM. Most patients with LAM develop breathlessness generally of insidious onset. Occlusion of lymphatics by LAM cells can lead to chylous pleural effusions or chylous ascites. In patients with advanced pulmonary disease hypoxaemia may develop. Pulmonary hypertension secondary to hypoxaemia is usually mild.

Imaging

The pulmonary cysts in LAM have a size usually varying from 2 to 30 mm and are distributed diffusely and bilaterally throughout normal lung parenchyma. Their shape is mostly round (Fig. 16.3). In severe disease the parenchyma is replaced by cysts with a reticular "lace-like" aspect.

Associated pneumothorax, or pleural effusion may be present.

In a series of 186 patients with TSC who had CT of the lung bases [57], thin wall cysts were found in 28 %. These were detected in 42 % of 95 females and also in 13 % of 91 males. Cysts were larger and more numerous in women than in men. Patients with TSC-LAM had, on average, slightly less severe lung disease than patients with sporadic LAM. Sixty-three percent of LAM patients had moderate to-severe disease compared with 40 % in TSC-LAM. Hepatic and renal AML and non calcified pulmonary nodules were more common in TSC-LAM, whereas lymphatic abnormalities (thoracic duct dilation, lymphangioleiomyomas) and chylous pleural and peritoneal effusion were more common in LAM.

Studies in a cohort of 293 patients from a TSC clinic provided more information on TSC-LAM according to the presence and type of mutations. Sixty-five patients with TSC were evaluated by chest CT [58] with cysts found in 49 % of women and 10 % of men. In the female population, changes consistent with LAM were present in 40 % with *TSC1* mutations, 48 % with *TSC2* mutation, and 71 % with no mutation identified. *TSC2* women with LAM had a greater number of cysts than *TSC1* women. Patients with TSC and no mutation have a higher incidence of both angiomyolipoma and LAM [59]. Among female patients with LAM, renal angiomyolipoma was universally present [60].

Multiple lung cysts may further be associated with multifocal micronodular lesions in TSC patients which consist of self-limited benign lesions with hyperplastic foci of large type II pneumocytes similar to atypical adenomatous hyperplasia of the lung, with a size up to 8–10 mm [61–63].

The imaging pattern of LAM at chest CT, although compatible and suggestive, is not pathognomonic and it can be mimicked by other lung conditions. The European Respiratory Society guidelines for the diagnosis and management of LAM recommended that a definite diagnosis be made in the presence of a characteristic CT scan (i.e. multiple >10) thin-walled round well-defined air-filled cysts with preserved or increased lung volume with no other significant pulmonary involvement especially no interstitial lung disease (with the exception of possible features of multifocal micronodular pneumocyte hyperplasia in patients with TSC) at CT scan, only when other supportive features of the disease are present namely, renal angiomyolipoma, TSC, a chylous collection or tissue biopsy from the lung or extra pulmonary sites consistent with LAM [64]. The combined prevalence of angiomyolipoma and lymphatic abnormalities mean that in over 50 % of cases an abdominal CT scan will be helpful in confirming the diagnosis of LAM without a lung biopsy [65]. A serum vascular endothelial growth factor-D (VEGF-D) level of greater than 800 pg/ml is found in approximately two-thirds of patients with LAM but not in other cystic lung diseases.

Patients with LAM generally have an accelerated loss of lung function with a rate of decline in forced expiratory volume in 1 s (FEV1) of 70–120 ml/year [66–68]. Some patients do not deteriorate over many years whilst others have a rapidly progressive course leading to respiratory failure within 5–10 years. Although at present there are no clear indicators of prognosis at diagnosis, presentation at a young age, an onset with breathlessness rather than pneumothorax, abnormal lung function at presentation including a low transfer coefficient for carbon monoxide (KCO) suggest more aggressive disease.

Pneumothorax is a particular problem for patients with LAM and early surgical intervention is appropriate. As the disease progresses patients develop worsening airflow obstruction, with 25 % of those partially responding to inhaled bronchodilators.

Overall, survival appears to be around 90 % at 10 years, with many patients having more longstanding disease [69].

Langerhans Cell Histiocytosis

Adult pulmonary Langerhans' cell histiocytosis (PLCH), formerly called histiocytosis X, is a rare bronchiolar disorder developing almost exclusively in young smokers [70, 71].

Pathology

The Langerhans cell has a dendritic shape, a clefted nucleus, and immunohistochemical staining with anti-CD1a antibody which distinguishes it from other histiocytes. A further characteristic feature is the identification of intracellular Birbeck's granules at electron microscopy.

The poorly demarcated granulomas formed by Langerhans cells extend from the bronchioles to the adjacent alveolar structures. The early cellular and granulomatous lesions are often centred on a cavity that is the residual lumen of the destroyed bronchiole. The end-stage lesions almost acellular consist of stellar fibrotic scars and/or cystic fibrous cavities [72].

Clinical Features

PLCH typically occurs in smokers 20–40 years old, with cough or progressive dyspnea on exertion, with pneumothorax leading to the diagnosis in about 10–20 % of patients. PLCH may also be diagnosed in a patient presenting with characteristic extra-pulmonary manifestations especially diabetes insipidus, cutaneous lesions, or osteolytic bone lesions. The lung function tests in PLCH may show airflow obstruction in patients with progressive disease. Reduction of carbon monoxide transfer factor is most common and may be severe. A discrepancy of subnormal FEV1/forced vital capacity (FVC) ratio with markedly decreased carbon monoxide transfer is common.

Imaging

On chest X-ray the pulmonary lesions predominate in the upper and middle lung fields (with sparing of the costophrenic areas). They consist of micronodular, reticular, or cystic features. CT imaging shows the presence of nodules (with a centrilobular distribution), cavitated nodules (thick-walled cysts), and thin-walled cysts. The nodules which are surrounded by normal parenchyma may be few or innumerable, with a size up to 20 mm. Cavitated nodules are very characteristic for PLCH. The thin-walled cysts often have bizarre irregular configurations with bilobed, cloverleaf, and branching morphologies.

Serial CT may typically show the characteristic sequence of nodules which cavitate into thick-walled cysts, and eventually thin-walled cysts. However the nodules may completely disappear without significant parenchymal sequelae.

In a series [73], the most common abnormalities consisted of micronodules ≤5 mm in diameter (89 %), thick-walled cysts (82 %), thin-walled cysts with walls of 2 mm or less (82 %), nodules (74 %), bizarre cysts (41 %), and reticulation (41 %).

Diagnosis and Management

The diagnosis of PLCH may confidently be established without lung biopsy when both cavitated nodules and thin-walled cysts are discovered on HRCT in young heavy smokers because of a pneumothorax or dyspnea, or when characteristic extra-thoracic features are present (isolated diabetes insipidus, or cutaneous involvement easily accessible to biopsy).

MCLD in Lymphoid Disorders

Lymphoid Interstitial Pneumonia

Lymphoid (lymphocytic) interstitial pneumonia results from diffuse reactive pulmonary lymphoid hyperplasia of bronchus-associated lymphoid tissue (BALT) with scattered plasma cells and histiocytes. Follicular bronchiolitis is a follicular hyperplasia of BALT present in the bronchiolar wall. LIP along with follicular bronchiolitis is considered as part of a spectrum of BALT hyperplasia related to connective tissue disease especially Sjögren syndrome [74] and other autoimmune disorders, and in infections with Epstein-Barr virus or human immunodeficiency virus.

Cysts were present in 15 patients in a series of 22 patients with LIP [75] including 6/10 with Sjögren syndrome (SS), 6/7 with Castleman disease, 1/2 with acquired immunodeficiency syndrome (AIDS), and 2/3 with no underlying disease. The average size of the cysts was 6 mm, these being bilateral in 10 and unilateral in 5. Other common findings in this series included areas of ground-glass attenuation and poorly defined centrilobular nodules in all the patients, subpleural small nodules, thickening of bronchovascular bundles, interlobular septal thickening, and lymph node enlargement.

In a large study [76] of 80 patients with Sjögren syndrome (56 primary including 11 with clonally derived lymphoproliferative disorder, and 24 secondary), cysts were present in 30 (22 in primary and 8 in secondary). Other CT findings consisted of interlobular septal thickening, intralobular reticular opacities, ground-glass opacities, honeycombing. The presence of cysts was independently and significantly associated with clonal lymphoproliferative disorder and anti-SSB antibody seropositivity. The mean number of cysts was 14, with a mean size of 16 mm, predominating in the lower and outer one-third zones.

Cysts in patients with primary SS were reported in 18/60 patients and were significantly associated with anti-SSB antibodies and clonally derived lymphoproliferative disorder [77]. Multiple bullae were present on CT imaging in only 3/32 patients with primary SS in another series [78]. Cysts in Sjögren syndrome are presented below (Fig. 16.4).

Pulmonary Lymphoma

Low-grade lymphoma of the BALT is a rare cause of MCLD. The distribution of the lesions is centred on the airways with features of bronchiolitis with possible associated

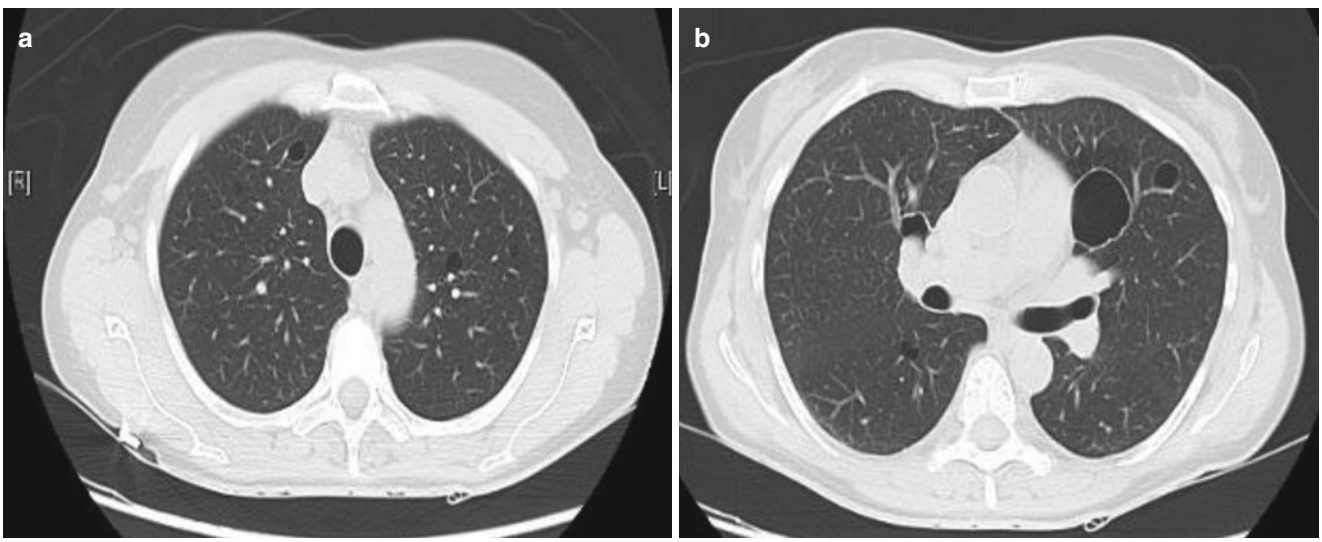

Fig. 16.4 Cysts in Sjögren syndrome. (**a**) Small intra-parenchymal round cysts. (**b**) More voluminous cyst in the same patient

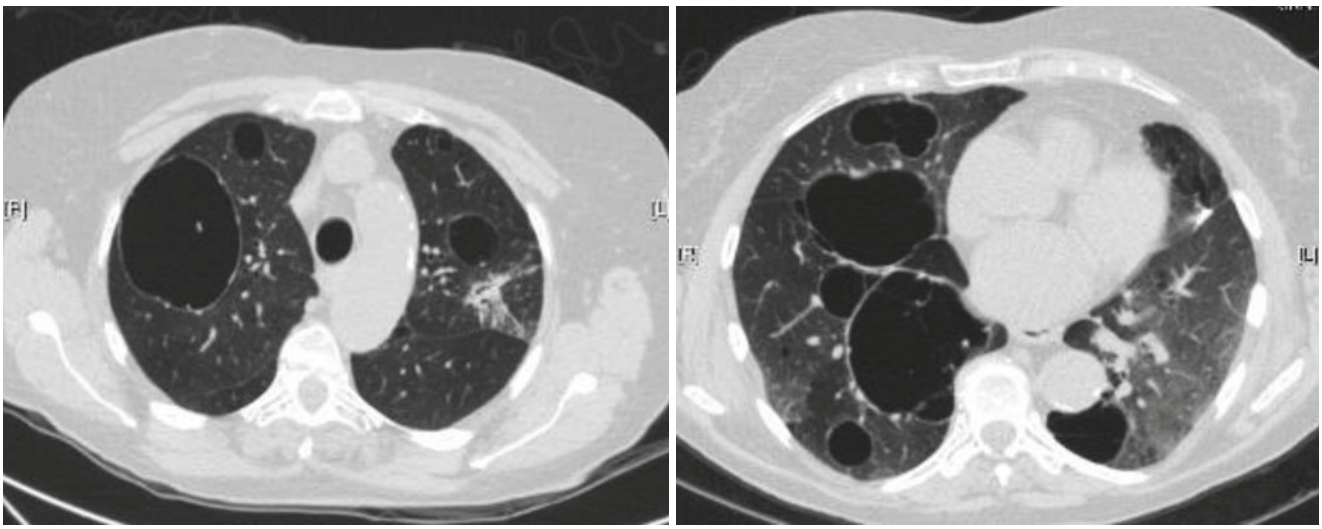

Fig. 16.5 Cysts in non-amyloid monoclonal immunoglobulin deposition disease (same patient)

airflow obstruction [79, 80]. BALT lymphoma is diagnosed by immunohistochemistry staining monotypic B cell markers. However the definite proof of clonal proliferation is obtained only by polymerase chain reaction-based DNA testing for immunoglobulin chains and T-cell gene rearrangements. A monoclonal gammopathy when present in the blood and/or urine may orientate the diagnosis.

Amyloidosis and Nonamyloid Immunoglobulin Deposition Disease

Amyloidosis

MCLD in isolated pulmonary lymphoma may be associated with amyloidosis [81]. The cystic lesions were found to correspond to dilated bronchioles infiltrated by amyloidosis. Multiple cysts associated with nodular amyloidosis (of the AL type) especially in Sjögren syndrome without systemic amyloidosis [82–85], and isolated multiple cystic pulmonary amyloidosis have been reported [86].

Diffuse alveolar septal amyloidosis with multiple cysts and calcification has only rarely been reported [87].

NonAmyloid Immunoglobulin Deposition Disease

Whereas light-chains of monotypic immunoglobulins may deposit in the tissues as fibrillar amyloidosis resulting from a β-pleated sheet configuration consequently binding Congo red, less commonly, light-chains may deposit in the tissues (especially the kidney) as an amorphous (non fibrillar) material [88].

Light chain deposition has been described in patients with MCLD referred for lung transplantation with a presumptive diagnosis of either PLCH or LAM. The disease was histologically characterised by non-amyloid deposits in the alveolar walls, the small-airways and the vessels (with further emphysematous-like changes and small airway dilation). Electron microscopy revealed coarsely granular deposits. Monotypic kappa light-chain fixation was demonstrated on the abnormal deposits and along the basement membranes [89]. Further using polymerase chain reaction a dominant lymphoid B-cell clone was identified in the lung with biological features suggesting antigen-driven primary pulmonary lymphoproliferative disorder [90]. A monoclonal immunoglobulin component may be identified in the blood and/or urine in a proportion of patients. The diagnosis of light-chain deposition disease may be obtained by pulmonary biopsy but also by bronchial biopsy in non-amyloid immunoglobulin deposition disease presenting as MCLD [91]. Mass spectrometry on formalin fixed paraffin-embedded tissue may confidently diagnose kappa light chain deposition disease [92]. Cysts in non-amyloid monoclonal immunoglobulin deposition disease are presented above (Fig. 16.5)

MCLD of Infectious Origin

Cysts of infectious origin are often referred to as pneumatoceles which result from an inflammatory process that causes central parenchymal necrosis, with a cystic expansion due to elastic retraction of the surrounding lung tissue. These often occur in patients in whom only a small area of bacterial pneumonia with consolidation was present. The cyst is frequently larger than the preceding infiltrate and characteriscally has thin walls.

Staphylococcal and Other Bacterial MCLD

Pneumatoceles develop rapidly and often resolve spontaneously [93].

Pneumonia due to *Staphylococcus aureus* especially common in the middle of the last century was characteristically associated with multiple pneumatoceles. The mere presence of pneumatoceles on chest X-ray was then commonly considered as diagnostic of staphylococcal pneumonia. They usually develop in the first week of pneumonia and disappear in an average of 6 weeks [94–97].

Pneumatoceles have also been reported in other bacterial pneumonias, especially in pneumococcal pneumonia in up to 19 % of cases [98].

Pneumocystis jiroveci Associated MCLD

Pneumocystis jiroveci pneumonia, occurring in immunocompromised patients, was a major cause of morbidity and mortality in patients with acquired immunodeficiency syndrome (AIDS) in the 1980s [99]. Since antiretroviral therapies have been available, the incidence of *P. jiroveci* pulmonary infection and mortality in AIDS in developed countries have dramatically decreased.

In AIDS patients the typical pulmonary features of *P. jiroveci* pulmonary infection consist of diffuse pulmonary ground-glass and/or reticular opacities usually without pleural effusion. Pulmonary cysts, thin or thick walled, with regular or irregular shape, may be present either isolated or more commonly associated with infiltrative opacities. Cysts may regress under highly active antiretroviral therapy [100].

In a comparative study [101] of *P. jiroveci* in 38 immunocompromised patients, those with AIDS had a higher proportion of cysts (56 vs 3 %, $p = 0.015$) and a lower proportion of ground glass attenuation 44 vs 86 % ($p = 0.02$). On multivariate analysis, only AIDS was a risk factor for the formation of cysts.

Recurrent Respiratory Papillomatosis

Recurrent respiratory papillomatosis (RRP) caused by human papilloma virus (HPV) especially types 6 and 11 develops in the upper airways especially the larynx. It usually presents in childhood and is thought to be acquired through vaginal birth, especially from mothers with condyloma. Tracheal and bronchopulmonary spread of RRP developed in only 1.8 % of a series of 448 patients with juvenile onset RRP [102]. The pulmonary lesions characteristically consist of bilateral multiple cavities, thin-walled cysts, and nodules predominating in the lower lobes [103–105]. The cysts are usually less than 5 cm in diameter, with occasional air-fluid level (resulting from superimposed infection). The destruction of the lungs by papillomatosis may occasionally be massive. Mortality from pulmonary papillomatosis is high resulting from the extensive cystic destruction of the lungs. Malignant transformation into squamous cell carcinoma may occur [106].

MCLD in Hyper-IgE Syndrome

The hyper-IgE syndrome is a primary immunodeficiency characterised by very high levels of Serum IgE (mean about 20,000 UI/mL), eczema, recurrent infections (especially pulmonary and cutaneous), with further connective tissue and skeletal abnormalities. Recurrent skin abscesses and pneumonia result mainly from *Staphylococcus aureus* infection. Mutations in the gene encoding the signal transducer and activator of transcription 3 in the type 1 of the syndrome (classic autosomal dominant or sporadic) have been reported [107].

Pneumonia onset ranges especially from the newborn period to 3 years, with the formation of cysts (solitary or multiple) up to 8 years after pneumonia. The size of the cysts may be up to 12 cm. They may resolve after prolonged antibiotic therapy. The histopathologic features of the cysts are those of chronic abscesses with a dense necrotic layer of exudates with leukocytic infiltration [108–110].

MCLD of Tumoural Origin

MCLD has been reported especially in patients with sarcoma and in patients with benign uterine leiomyoma.

Metastases of Sarcomas

Pneumothorax may be the presenting manifestation of an extrapulmonary sarcoma with cystic metastases [111, 112]. Pneumothoraces in patients with pulmonary cystic metastases from sarcoma have been reported in patients with angiosarcoma [113–116], epithelioid sarcoma [117–120], leiomyosarcoma [112], osteosarcoma [121]. The wall of the cysts is usually composed of tumor cells.

The size of the cysts may be up to about 7 cm. Air-fluid level which may be present in the cysts correspond to blood or organising clots.

Multiple cystic lung metastases, presenting as pneumothorax (possibly bilateral), have been reported in endometrial stromal sarcoma [122].

Metastases of Benign Uterine Leiomyoma

Benign metastasizing leiomyoma to the lung may develop after enucleation or total myomectomy for benign uterine leiomyoma. The pulmonary metastases may present as nodules or masses, or as cysts the walls of which are composed of smooth muscle spindle-shaped cells lined by epithelium [123–125]. The spindle cells stain positive for alpha-smooth muscle actin, desmin, oestrogen and progesteron receptors, and negative for HMB-45 [123, 125].

Other Malignancies

MCLD from "benign" metastatic meningioma has been reported [126].

Spontaneous bilateral pneumothorax with multiple cystic metastases from renal cell carcinoma on sunitinib therapy has also been reported [127].

Other Causes of MCLD

Congenital Cystic Disorders

Congenital cystic lung disease comprises congenital cystic adenomatoid malformations (CCAM) renamed congenital pulmonary airway malformations (CPAM) because only the CCAM of types 1, 2 and 4 are cystic indeed [128–130].

CPAM type 1 (60–70 % of cases) is composed of cysts ranging 1–10 cm in size, usually limited to one lobe, rarely multiple or bilateral. They appear to be primarily of bronchial and bronchiolar origin. CPAM type 2 is composed of multiple small cysts, 0.5–2.0 cm in diameter, that resemble bronchioles, and associated in about 50 % of cases with other severe anomalies (e.g. renal agenesis or diaphragmatic hernia) [131]. The cysts blend with the normal parenchyma. CPAM type 4 is composed of large cysts up to 10 cm resembling distal acina structures [63]. The cysts are lined with flattened type 2 alveolar lining cells with the wall of the largest cysts composed of loose mesenchymal tissue. More than half of children with CPAM present with respiratory manifestations in the neonatal period leading to surgical resection.

Interstitial Lung Diseases

In the interstitial lung diseases other than lymphoid interstitial pneumonia MCLD is only exceptionally a prominent feature.

In hypersensitivity pneumonitis lung cysts have been reported in 13 % of a series of 182 patients with subacute hypersensitivity pneumonitis [132]. Their size ranged from 3 to 25 mm, and their number from 1 to 15, with a random distribution. Diffuse ground-glass opacification was also present in all patients.

Desquamative interstitial pneumonia (DIP) is a smoking-related disorder characterised by intra-alveolar accumulation of macrophages containing pigment. The CT imaging features of DIP are characterised by diffuse ground-glass opacities especially in the middle and lower lung zones, with further features suggestive of fibrosis. Associated cysts have been reported [133–137] in up to 32 % in a series of 22 patients [133].

MCLD of Genetic Origin

Neurofibromatosis

Thin-walled cysts (3 to more than 100) especially in the upper lobes have been reported in patients with type I neurofibromatosis, in association with ground-glass opacities [138, 139].

Ehlers-Danlos Syndrome

Multiple thin-walled cysts with air fluid levels and multiple solid nodules have been reported in type IV Ehlers-Danlos syndrome [140].

Proteus Syndrome

Proteus syndrome is a sporadic congenital disorder with asymmetric and disproportionate overgrowth of body parts, connective tissue, and vascular malformations. Joseph C. Merrick, the so-called famous Elephant Man, might have been affected by this syndrome. It is caused by a somatic activation in the oncogene *AKT1*. Pulmonary cystic malformations present in about 10 % of cases are part of the diagnostic criteria of the syndrome [141–143]. They consist of multiple thin- and thick-walled cysts and emphysematous hyperexpanded airspaces of all sizes, with possible severe consequences.

Others

Small subpleural lung cysts (0.1–0.4 cm, up to 1 cm) usually asymptomatic have been reported in newborn children with Down syndrome [144]. These are lined with cuboidal cells, with a distribution along the pleural surfaces, at the periphery of lung lobules, and deep in the parenchyma.

Lung cysts on CT were associated with dilation of terminal bronchioli and alveolar duct in lung biopsies in 6 out of 15 patients children with surfactant protein C gene mutation-associated lung disease [145].

Cysts and ground-glass opacities have been reported in subtype B Niemann-Pick disease [146].

Mesenchymal cystic hamartomas of the lung have been reported in Cowden's disease [147].

Other MCLD

Posttraumatic pseudocysts (pneumatocele) may result from blunt trauma with laceration of the lung [148] especially in children and young adults [149]. They are more often single,

but they may occasionally be multiple (unilateral or bilateral) or pluriloculated, and may be filled partially with blood. Their size usually decreases progressively within a few days or weeks to eventually disappear [150].

Blebs/bullae represented respectively 39 and 88 % of pathologic findings in a series of 114 patients with catamenial and non-catamenial pneumothorax, and in 48 % of 29 endometriosis related pneumothorax (all on the right side) [151].

Mechanisms of Cyst Formation

Several mechanisms of cyst formation have been proposed, however most of these remain speculative and they only partially explain how very dissimilar disorders share MCLD as a common denominator [152].

Chronic small airway disease of various origin may cause MCLD possibly because of check-valve mechanism. They further include vascular occlusion or ischaemia necrosis, and dilation of the bronchioles. Degradation of the connective matrix especially by metalloproteinases may play a further role especially in LAM and PLCH.

Diagnosis of MCLD

The discovery of more MCLD especially in asymptomatic or paucisymptomatic patients has especially benefited of the advent of HRCT [152–156].

Although MCLD may be suspected on chest X-ray only HRCT allows to analyse appropriately the features of the cysts and the possible associated abnormalities. MCLD may be found in a patient with pneumothorax (the major clinical presentation of many MCLD) especially when relapsing, in screening a patient with manifestations of a systemic disorder (previously diagnosed or not) as LCH or TSC, or in patients with chest X-ray showing abnormal findings.

Recurrent pneumothorax in any patient should always requires the search for a possible underlying disorder especially MCLD. Screening for LAM by CT in young non-smoking women age 25–54 presenting with spontaneous pneumothorax was cost-effective in one study [157].

There is usually no difficulty to identify *cysts* on HRCT, however it may sometimes be difficult to distinguish genuine cysts from cavities or cavitary nodules.

The two major differential diagnoses of MCLD at HRCT imaging are advanced centrilobular emphysema and cystic bronchiectasis (especially in the upper lobes where these lie adjacent to vessels and are branching). Further cystic bronchiectasis may associate with emphysema in patients with emphysema [158].

Occasionally air trapping on expiration [159] resulting from the occlusion or the narrowing of the small airways may mimic cysts [160].

The aetiologic diagnosis of MCLD is facilitated in many cases based on discriminant characteristics as gender (sporadic LAM may be excluded in a man), systemic manifestations of an associated systemic disorder with definite features (either of genetic origin or acquired). However the manifestations of associated disorders may be overlooked and thus these need to be systematically searched for. For example a retrospective cohort study of patients 18 years or older with TSC reported that diagnosis was made only in 59 % of adult patients. Patients with delayed diagnosis had less seizures but more LAM and angiomyolipoma at the time of TSC diagnosis than those with TSC diagnosed in childhood [161]. Lung biopsy is indicated in only a minority of patients especially those with evolutive MCLD requiring definite diagnosis for treatment. Although the aetiologic diagnosis is eventually obtained in almost all MCLD, few patients have definite or no diagnosis even after lung biopsy.

Table 16.2 summarises the distinguishing features of the big three MCLD.

Table 16.3 is a check-list of clinical manifestations and tests to be systematically considered in the aetiological diagnosis of MCLD.

As pneumothorax is a common manifestation in patients with MCLD (especially in LAM and *FLCN*-S) any exposure to large ambient pressure differences could precipitate its occurrence. Patients should abstain from air travel if new respiratory symptoms have appeared, or if they have a known persistant pneumothorax, or a pneumothorax treated within the previous month. Deep-sea diving, plane piloting, high-mountain climbing may be contra-indicated.

Conclusion

The MCLDs are increasingly recognised as a diagnostic challenge. They were initially recognised in their more caricatural features on chest X-ray and analysed by the pathologists especially at necropsy. The major change occurred once CT imaging (especially HRCT) became available thus allowing more precise recognition of MCLD. The variety of causes of MCLD has progressively been recognised. Any chest physician presently has to diagnose MCLD including its cause, and to refer in most cases the patient to an expert centre for confirmation of diagnosis and further management.

Summary

Multiple cystic lung disease (MCLD) is defined by the presence of multiple round parenchymal lucencies of low-attenuating area with a well-defined interface with normal lung, with a wall thickness usually less than 2 mm. The big three causes of MCLD are lymphangioleiomyomatosis either sporadic or associated with tuberous sclerosis, pulmonary

Table 16.2 Distinguishing features of lymphangioleiomyomatosis (*LAM*) sporadic or associated with tuberous sclerosis complex (*TSC*), pulmonary Langerhans cell histiocytosis (*PLCH*), and FLCN-associated syndrome (*FLCN*-S)

		LAM		
	FLCN-S	S-LAM	TSC-LAM	PLCH
Gender	F,M	F	F,M (rare)	F,M
Smoking	±	±	±	+++
Pneumothorax	+++	+++	++	++
Familial history of pneumothorax	+++	–	–	–
Pleural effusion	–	+	+	–
Airflow obstruction	–	+++	++	+++
Low KCO	–	+++	+++	+++
Respiratory failure	–	+++	++	++
Severe pulmonary hypertension	–	–	–	+
Skin manifestations	+++ [18]	–	+++ [162]	+
Renal tumours				
Angiomyolipoma	–	++	+++	–
Malignant tumours	++ [163]	–	± [163]	–
Lymphangiomas	–	++	+	–
Bone lesions		–	+ (sclerotic, lytic) [164]	+ (lytic)
Others	+[a]	–	+[b]	+[c]

[a]Other features comprise the co-occurrence of various benign or malignant tumours (e.g. colorectal polyps or cancers). An increased risk of such tumours in specific subgroups of patients cannot be excluded [18]
[b]Other features in TSC comprise especially cerebral features (especially seizures, cognitive impairment, behavioural problems, cortical tubers, giant cell astrocytomas), multiple retinal nodular hamartomas, renal cysts [162, 165]
[c]Other features comprise especially hypothalamo-pituitary involvement (diabetes insipidus with polyuria and polydypsia)

Table 16.3 Check-list for aetiologic diagnosis of MCLD

1. Evaluation of the circumstances of HRCT diagnosis of MCLD (e.g. pneumothorax)
2. Detailed analysis of HRCT features including the cysts (number, location, shape), but also possible associated parenchymal abnormalities, pleural abnormalities (pleural effusion uni-or bilateral, pneumothorax), mediastinal abnormalities, bone abnormalities
3. History (individual and familial) of pulmonary manifestations (especially pneumothorax) or extrapulmonary especially for TSC, PLCH, *FLCN*-S. Check with the list of causes if the history of the patient might fit with any of the diagnoses (e.g. ask the patient for the presence of xerostomia or xerophtalmia suggestive of Sjögren syndrome)
4. Consider other HRCT imaging of the head and the abdomen (e.g. cerebral features for TSC; angiomyolipoma of the kidneys or lymphangiomas of the abdomen for S-LAM or TSC-LAM)
5. Biological tests oriented according to the previous investigations or systematic
Auto-immune biology. Antinuclear or antinucleolar antibodies (with further characterisation if present), anti-CCP antibodies
Immunoglobulinic abnormalities. Serum and urine electrophoresis with immunofixation, search for cryoglobulin and characterisation, serum measurement of free immunoglobulin light kappa and lambda (with their ratio)
Measurement of VEGF-D in serum
Gene molecular analysis of *FLCN* and *TSC* genes
6. Lung pathology
Videoassisted lung biopsy is not aggressive but it is not necessary if a confident diagnosis may not be obtained otherwise. If a biopsy is done the specimen should obviously include cystic lesions. The lung biopsy should be examined by a lung pathologist experienced in diffuse lung diseases at a referral centre. The pathologist must be aware of all the aetiologic variety of MCLD. It is of utmost importance that frozen material be available for further diagnostic procedures as required

Langerhans cell histiocytosis, and the increasingly diagnosed *FLCN*-syndrome (Birt-Hogg-Dubé).

These disorders are associated with extrapulmonary manifestations which may strongly contribute to diagnosis. The other causes of MCLD include lymphoid disorders of the lung (especially in Sjögren syndrome), with further the recently described of non-amyloid immunoglobulin deposition disease; infections; malignancies especially metastases of sarcomas; hypersensitivity pneumonitis; desquamative interstitial pneumonia and a variety of other disorders.

MCLD is a rare CT imaging syndrome often associated with pneumothorax resulting mostly from rare "orphan" disorders.

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Lymphangioleiomyomatosis

17

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 to 7.8/million women with an incidence of 0.23 to 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 was 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 gaunosine tri-phosphatase 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 and gene translation; and with rictor and others in mTORC2 which has other less well defined functions but has a role in control of cytoskeletal arrangement and migration via the GTPase Rho [5] (Fig. 17.1. For a detailed description see reference [6]). Loss of TSC-1/2 function by a combination of genetic mutations or possibly epigenetic modifications results in constitutive activation of mTORC1 and hence uncontrolled proliferation, abnormal migration and other abnormalities within affected cells [7]. These cells, termed LAM cells, arise from an unknown precursor but form a proliferative clone capable of migrating throughout the body having a predilection for the lungs, lymphatics and kidneys. Drugs which block the activity of the mTORC1 complex are a promising treatment option for some patients [8]. LAM cells have an unusual phenotype, expressing proteins of smooth muscle lineage (α-smooth muscle actin, desmin) but also melanoma related antigens (GP100) suggesting a possible developmental origin in the neural crest [9].

Interestingly, 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 [10] leading to the 'benign metastasis model' of LAM pathogenesis [11]. Consistent with the idea that LAM cells arise from a single precursor which then spread throughout the body, LAM cells have been identified in blood, chyle and urine of patients with LAM [12].

Possibly in keeping with the female preponderance of the disease, LAM cells express receptors for oestrogen and progesterone [13]. In model systems, oestrogen promotes LAM cell growth and metastasis however anti-oestrogen therapies have not proven effective for patients [14, 15]. A major clinical aspect of the disease 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

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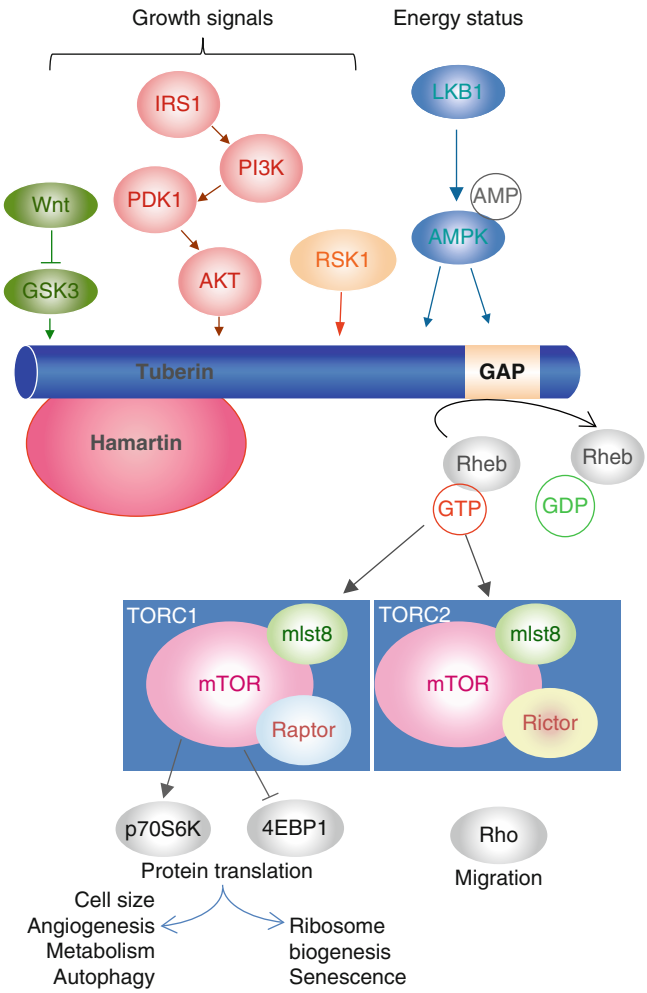

Fig. 17.1 Schematic representation of the mTOR pathway. Tuberin is phosphorylated by multiple inputs from growth signals via growth factors or as a consequence of change in cellular energy status. Phosphorylation of tuberin leads to increased guanine nucleotide hydrolysis via tuberin's GAP domain. Conversion 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

cells. Consistent with this idea, it has been shown that LAM cells produce a number of proteases including plasmin [16], cathepsin K [17] and matrix metalloproteinases-1, -2, -9 and -14 [18, 19]. These proteases are capable of degrading extracellular matrix proteins including collagens, elastin and proteoglycans. They can also contribute to the disease by activating growth factors, modulating cell surface receptor activity, inflammatory cell trafficking, angiogenesis and cellular invasion. As specific drugs targeting some of these proteins are available they have potential as therapeutic agents.

LAM nodules are complex structures comprised of multiple cell types including LAM cells, HMB45 negative stromal cells, lymphatic endothelial cells forming central lymphatic clefts, and covered by hyperplastic type 2 pneumocytes. The interactions between the various cell types and the identity of the stromal cells within the nodules remain to be elucidated. 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 a metabolic signature similar to that of cancer cells [20], LAM is viewed by some as a slow growing cancer or cancer-like disease. The processes contributing toward the pathogenesis of LAM are summarised in Fig. 17.2.

Presentation

LAM can manifest itself in a number of ways. Most commonly respiratory symptoms are the presenting problem, 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 approximately 80 % of patients. Around 5 % of patients present with chylous pleural effusions due to obstruction of the thoracic duct by LAM cells [1]. Chylous effusion and lung cysts in women being pathognomonic of LAM. Some patients cough chylous secretions due to blockage of the intrapulmonary lymphatics 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 [21].

Occasionally abdominal disease may present before lung symptoms. Most commonly this is with symptomatic renal angiomyolipoma. 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. In some patients, symptomatic angiomyolipoma has preceded lung symptoms by many years. 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 [22]. In a small number of cases, discovery of

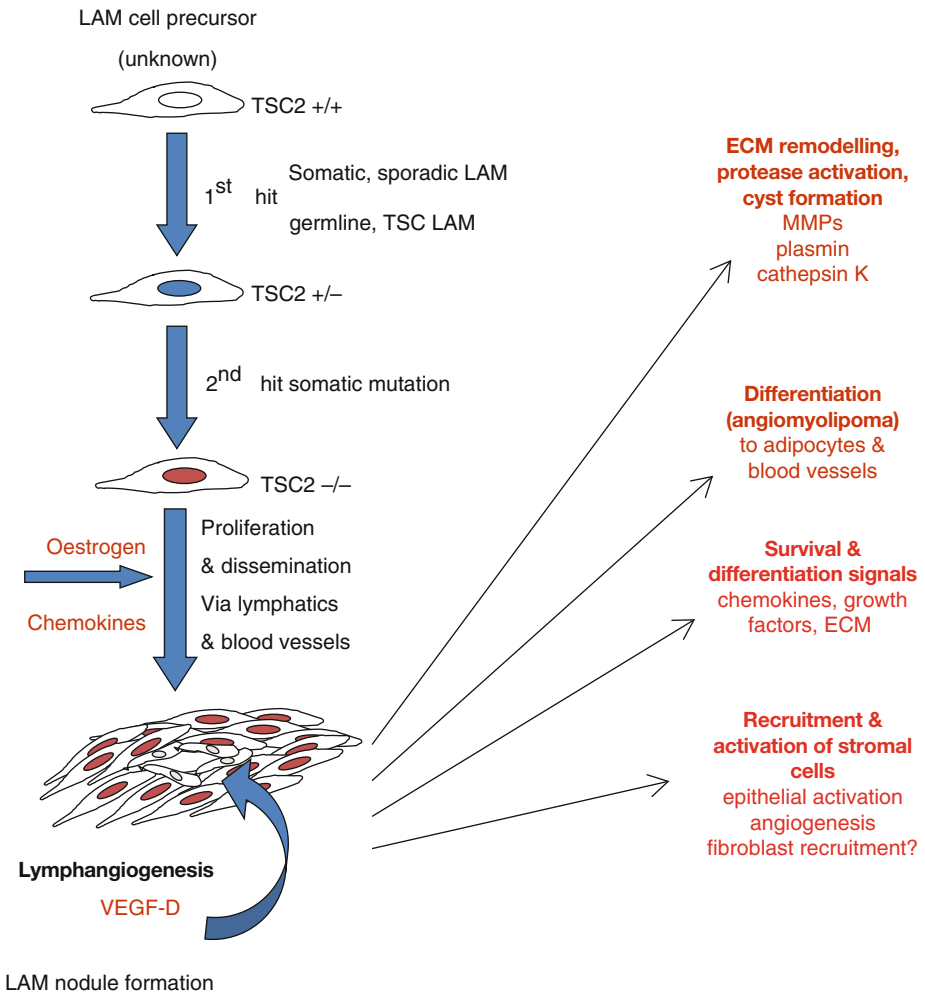

Fig. 17.2 Cellular and pathologic events contributing to the development of LAM. Biallellic inactivation of TSC-2 results in loss of functional tuberin protein in the LAM precursor cell. This confers a survival advantage and metastatic capability which is likely to be oestrogen dependent. LAM cells disseminate and form nodules acting as foci for lymphangiogenesis. The LAM nodule provides a supportive environment for LAM cell growth, is likely to recruit stromal cells, possibly allowing differentiation into the other components of angiomyolipoma including blood vessels and adipocytes. The production of proteases is likely to result in cyst formation and support further LAM cell dissemination. *ECM* Extracellular Matrix

these masses may lead to a biopsy for suspected malignant disease often resulting in chylous leakage with 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 advanced disease.

Up to 40 % of adult women with TSC have LAM when examined by CT scanning although only a minority of these develop symptomatic respiratory disease [23–25]. 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 [26]. 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 [27]. Lymphatic disease appears less common in TSC-LAM than sporadic disease [28]. Clinical presentations suggestive of LAM are listed in Table 17.1.

Table 17.1 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

Clinical 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 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.

Diagnosis and Workup

Interstitial changes and preserved lung volumes may be present on chest radiograph (Fig. 17.3) 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 [29] (Fig. 17.4). Widespread alveolar shadowing however is not typical of LAM. Chylous pleural effusions and pneumothorax may also be present (Fig. 17.5). In patients with TSC, nodules of proliferating type 2 pneumocytes, termed multifocal micronodular pneumocyte hyperplasia, may coexist with LAM or occur without LAM [30]. 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. Either, the presence of renal angiomyolipomas, chylous pleural or abdominal effusions, lymphatics involved by LAM or the presence of TSC. The European Respiratory Society has recently developed clinical guidelines for LAM and their diagnostic criteria are summarised in Table 17.2 [31]. 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 the key skin manifestations, facial angiofibromas, periungual fibromas, hypomelanotic macules and shagreen patches. In some patients, these abnormalities are mild 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 [32] 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 [31].

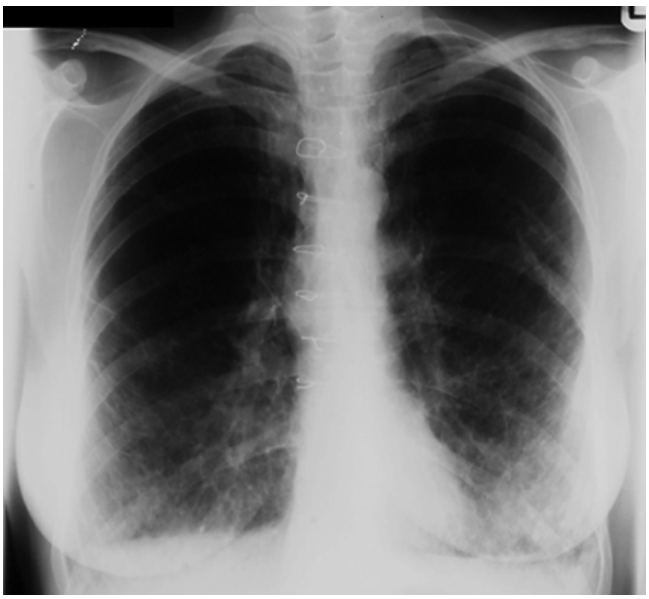

Fig. 17.3 Chest radiograph of a patient with advanced LAM. Reticular shadowing with preserved lung volumes

Pulmonary function testing may be normal in early disease but a fall in DLCO is generally the first abnormality that develops [33]. As the disease progresses airflow obstruction develops. Lung volumes are generally preserved [34]. Cardiopulmonary exercise testing provides more information on physiological derangement in early

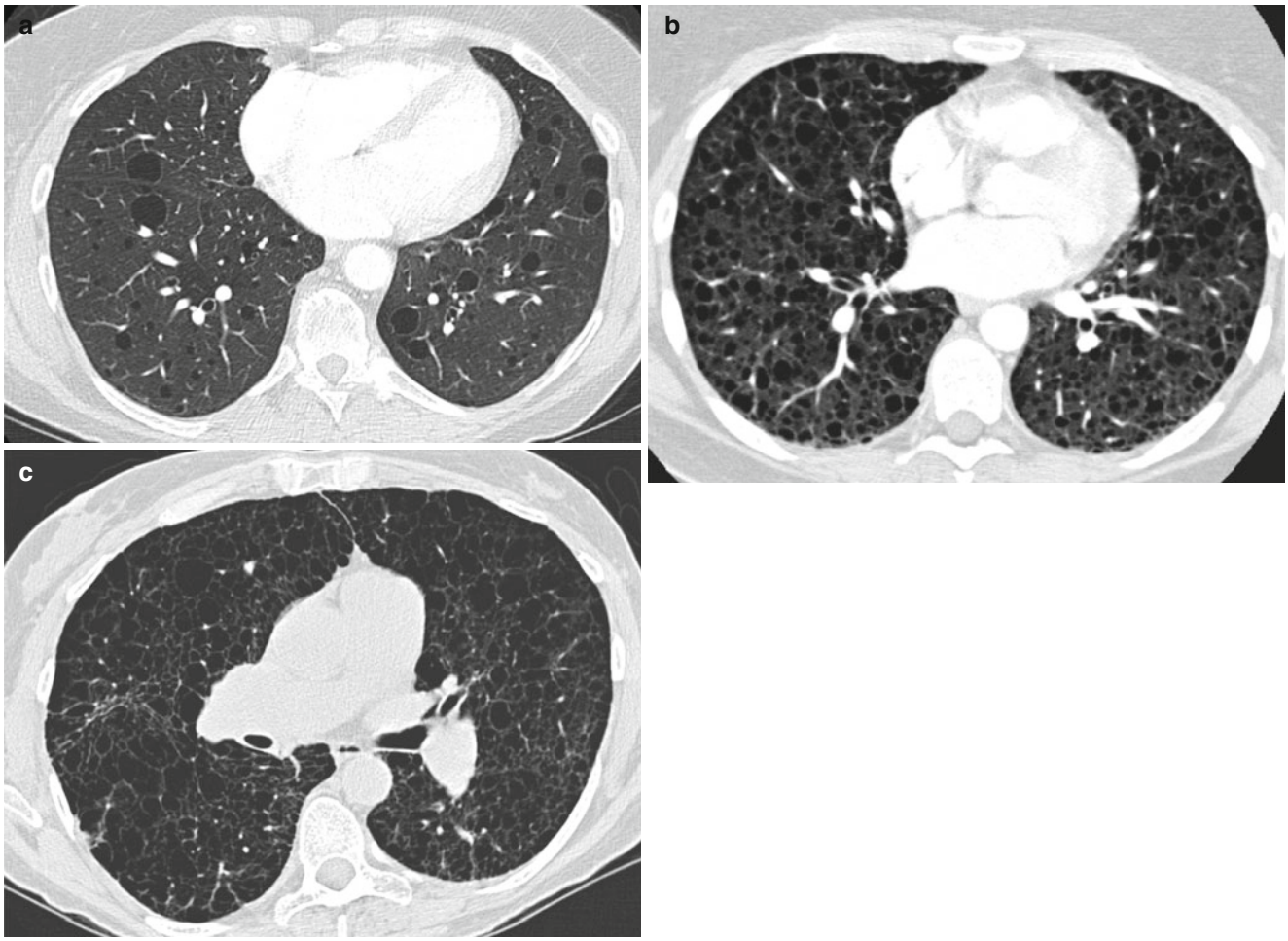

Fig. 17.4 High resolution CT appearances in LAM. (**a**) Shows a patient with very slowly progressive disease who has normal spirometry and mildly reduced gas transfer. (**b**) Shows a patient with progressive LAM with significant airflow obstruction and impaired gas transfer. (**c**) Shows advanced lung disease with very little lung parenchyma visible

disease although is seldom performed [35]. The 6 min walk test probably provides more 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 screened by MRI scanning in one series [36]. 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 [31].

A definite diagnosis of LAM according to ERS criteria can be made without lung biopsy in around 2/3 of patients [37]. In the remainder, 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 [31]. 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 [38, 39]. 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. 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

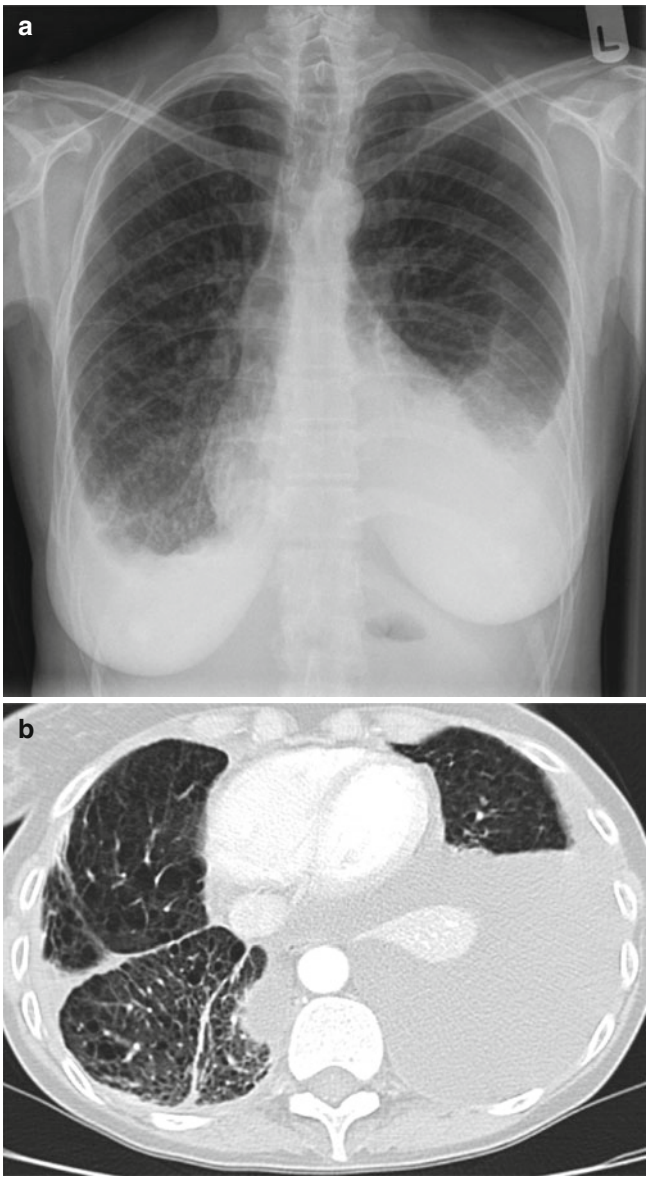

Fig. 17.5 Chylous complications. (**a**) Chest X-ray and (**b**) CT from the same patient showing bilateral pleural effusions and parenchymal changes due to LAM

detection can be improved by immunostaining for the smooth muscle markers α-smooth muscle actin and desmin, oestrogen and progesterone receptors [40, 41] (Fig. 17.6). HMB45 stains 30–70 % of LAM cells in biopsy tissue. HMB45 is particularly useful diagnostically, not being expressed in normal lung. Only isolated reports have described cases with the morphological characteristics of LAM in tissues biopsy that do not stain with HMB45.

Recently it has been observed that the lymphatic growth factor, vascular endothelial growth factor-D (VEGF-D) is elevated in around 2/3 of patients with LAM, particularly those with lymphatic involvement [42]. A serum VEGF-D level of greater than 800 pg/ml has been shown to differentiate LAM from other cystic lung diseases and when used in combination with the ERS diagnostic criteria, can further reduce the need for lung biopsy for diagnosis [37, 43]. At the time of writing, the test is not routinely available in all centres.

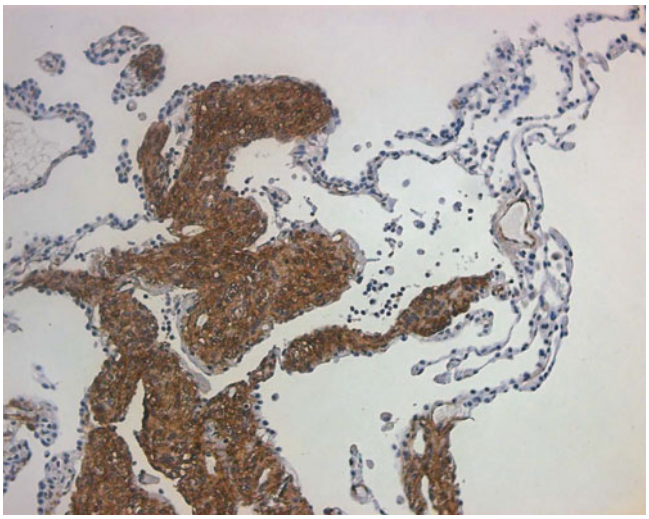

Fig. 17.6 Histological appearance of LAM. Lung section showing lung infiltrated by nodular proliferations of LAM cells which stain strongly for the smooth muscle marker, α-smooth muscle actin (*brown*)

Table 17.2 European Respiratory Society diagnostic criteria for LAM

Definite LAM
Characteristic or compatible[a] lung HRCT, and lung biopsy fitting the pathological criteria for LAM[a]
or
Characteristic lung HRCT and any of the following: angiomyolipoma (kidney); thoracic or abdominal chylous effusion; lymphangioleiomyoma or lymph-node involved by LAM; definite or probable TSC[a]
Probable LAM
Characteristic HRCT and compatible clinical history[a]
or
Compatible HRCT and any of the following: angiomyolipoma (kidney), thoracic or abdominal chylous effusion
Possible LAM
Characteristic or compatible HRCT

[a]See Ref. [31] for details

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 likely that presentation with breathlessness rather than pneumothorax, a response to bronchodilators, low K_{CO} at presentation and extensive involvement of the lung biopsy with either cystic change or muscular proliferation are associated with more rapid disease progression [44–47]. 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. 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 to be between 20 and 30 years. 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 and pneumococcus and in those limited by dyspnoea undertake pulmonary rehabilitation. 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.

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), France (http://asso.orpha.net/FLAM/), the USA (www.thelamfoundation.org) and others. In addition rare disease organisations such as Orphanet (http://www.orpha.net/consor/cgi-bin/index.php) provide disease specific information for patients.

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 120–150 ml/year [34, 48], those with loss of lung function due to progressive parenchymal disease, rather than pleural complications, should be seen more frequently and therapy with an mTOR inhibitor considered.

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 [49]. Surgical intervention reduces recurrence rates and should be considered after the patient's first pneumothorax. Evidence is only available from case series but suggests that surgical approaches may be more effective than pleurodesis via chest tube [21, 49]. In a significant number of cases, more than one surgical procedure may be 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 [50] and patients with pneumothorax should be treated with the most appropriate surgical procedure to treat pneumothorax.

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 reaccumulation of the fluid [51]. Rates of fluid formation may be reduced by a low fat, or medium chain triglyceride, diet however in many cases surgical pleurectomy and possibly thoracic duct ligation may be required. Recently, use of the mTOR inhibitor rapamycin has been shown to reduce the volume of chylous pleural effusions and reduce the need for thoracocentesis in these patients [52].

Renal Angiomyolipoma

Patients with angiomyolipomas should have their renal tumours monitored regularly. Once initial cross sectional

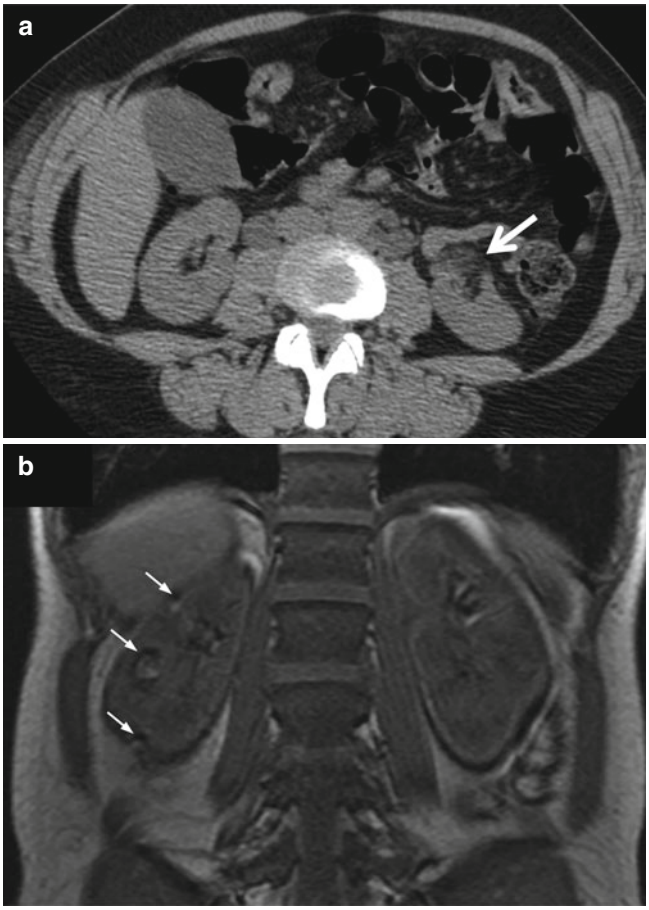

Fig. 17.7 CT appearances of angiomyolipoma in patients with sporadic LAM. (**a**) Shows a characteristic small asymptomatic lesion in the anterolateral aspect of the left kidney (*arrow*). The low density areas containing fat are characteristic of angiomyolipoma. (**b**) Coronal section of a T1 weighted MRI image showing multiple small angiomyolipomas in the right kidney (*arrows*)

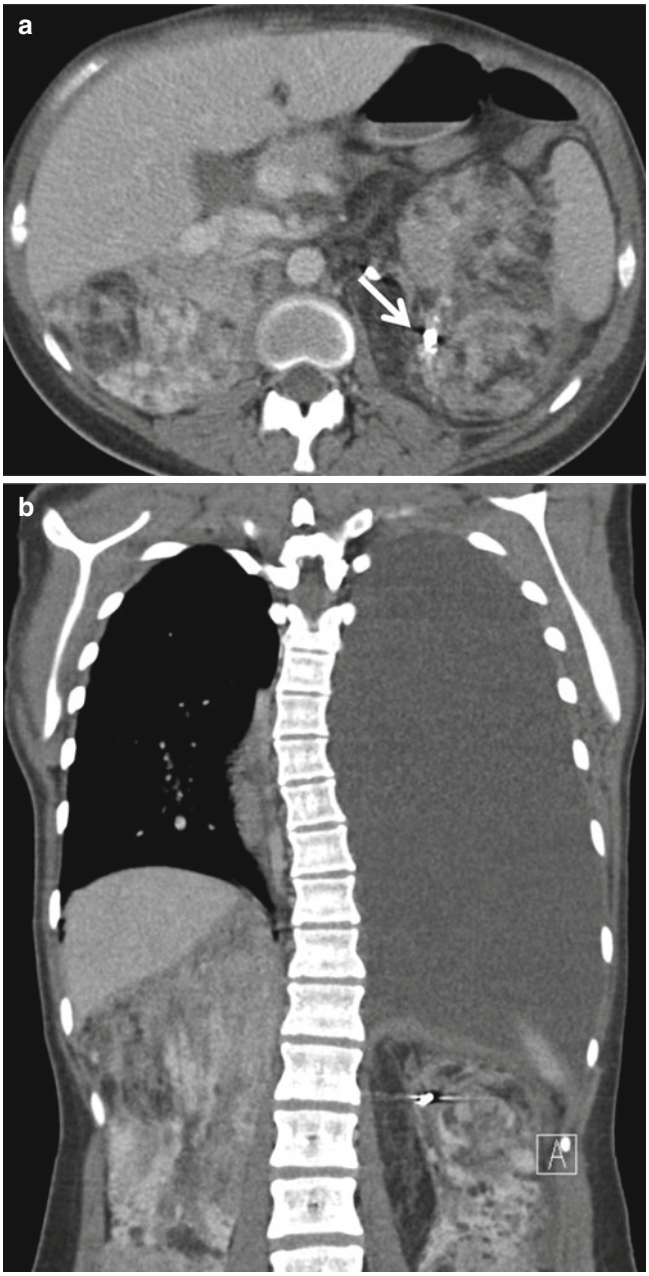

Fig. 17.8 Angiomyolipomas in TSC-LAM. (**a**) Shows a cross sectional image of a patient with TSC-LAM and multiple, bilateral angiomyolipomas greatly enlarging both kidneys. The *arrow* highlights an embolisation coil, used to treat a bleeding lesion. (**b**) Shows a coronal CT of the same patient who presented with dyspnoea due to a large left chylous effusion

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. 17.7). 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 imaged at 6 monthly intervals [53]. Large, enlarging and symptomatic tumours should be evaluated by a urologist, ideally with expertise in conservative management of these lesions. As angiomyolipomas are frequently bilateral, selective treatment of large and symptomatic lesions may be performed by conservative nephron sparing surgery or by selective transcatheter embolisation rather than nephrectomy. Outcomes are similar between techniques although embolisation may be performed without the use of a general anaesthetic including during episodes of haemorrhage and pregnancy [54]. Those with TSC-LAM almost always have renal angiomyolipomas. These tend to be bigger and more likely to bleed than those in patients with sporadic LAM [27] (Fig. 17.8).

Abdominopelvic Lymphatic Disease

Occlusion of the axial lymphatics by LAM cells can result in enlarging cystic structures. Although often asymptomatic,

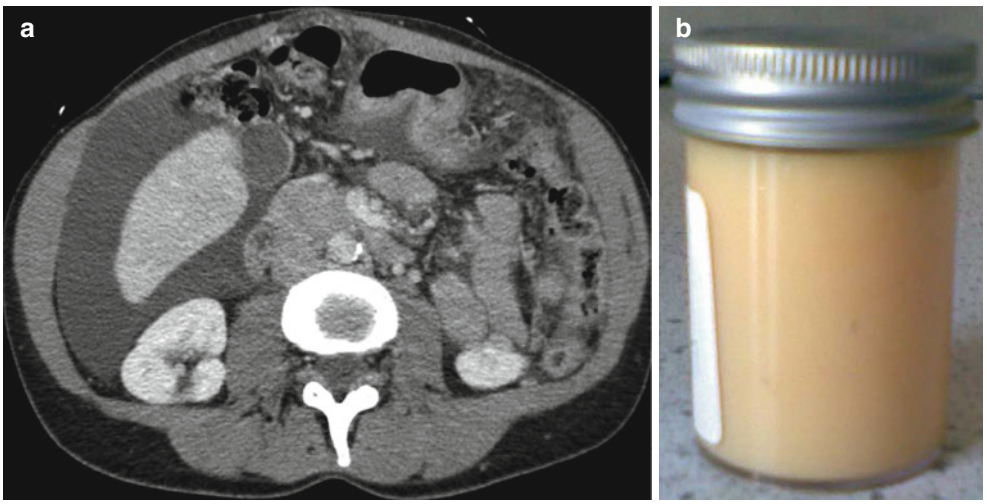

Fig. 17.9 Abdominal lymphatic disease. (**a**) CT shows dilated retroperitoneal lymphatics and chylous ascites. (**b**) Shows the appearance of chylous fluid from a patient with LAM

these lesions can be associated with abdominal distension and bloating [55]. Characteristically these lesions enlarge throughout the day, which can be associated with worsening symptoms in the afternoon [56]. 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. 17.9). Surgical treatment of abdominal lymphatic masses can be followed by prolonged chylous leakage and is best avoided. Symptomatic measures include reducing fat intake as for chylous pleural effusions. Recently case reports and a case series have suggested that treatment with mTOR inhibitors is effective for symptomatic abdominopelvic lymphatic disease resulting in resolution of symptomatic chylous ascites and lymphangioleiomyomas [52].

Pregnancy

During pregnancy, women with LAM have an increased risk of pneumothorax, chylous effusion and possibly bleeding angiomyolipoma [21]. 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 the patient's initial 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 [57].

Tuberous Sclerosis

Patients 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 [58]. 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 17.3 [26]. Those requiring genetic counselling, those with symptomatic epilepsy, 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, 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 [59, 60].

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. 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 adults with TSC has identified many of these patients with mild disease and

Table 17.3 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	Electrocardiography
	If cardiac dysfunction occurs	Echocardiography
Renal angiomyolipomas and cysts	At diagnosis	Renal ultrasonography
LAM	Women in adulthood and if pulmonary dysfunction occurs	High resolution CT
Cerebral hamartomas and tumours	At diagnosis	Cranial MRI or CT

Adapted from Ref. [26]

their management should involve general measures for LAM such as advice about pneumothorax and oestrogen avoidance however they may require different prognostic advice and less frequent follow up [31]. In addition, 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 [21, 45]. A trial of beta agonists is suggested in these patients.

LAM cells have constitutive activation of the mTORC1 complex and in a randomised placebo controlled trial the mTOR inhibitor rapamycin (Sirolimus) has been shown to reduce decline the in FEV_1 of patients with impaired lung function [48]. Rapamycin also reduces the volume of angiomyolipomas [61, 62] and sub ependymal giant cell astrocytomas in patients with TSC [63]. Trials of other mTOR inhibitors and in other indications in patients with TSC are currently underway. mTOR inhibitors cause side effects in the majority of patients treated, particularly mouth ulcers, hyperlipidaemia, nausea, diarrhoea, proteinuria and peripheral oedema. An increased susceptibility to infections and an iatrogenic pneumonitis are also possible. For LAM, rapamycin is generally dosed to achieve a serum level of 5–10 ng/ml. The number of side effects, need for serum level monitoring and a number of drug interactions means that these patients need careful monitoring during therapy and are best used in centres with experience of their use and monitoring. Current indications for use of mTOR inhibitors in LAM include rapid decline in FEV_1 due to parenchymal lung disease (rather than pneumothorax or pleural surgery) [48], chylous collections unresponsive to other therapies [52] and angiomyolipoma endangering renal function which are not suitable for surgical therapy [62]. There are also various indications for patients with TSC. The role of rapamycin in patients with very advanced disease is currently not well defined. Few of these patients have been included in clinical trials and they are unlikely to benefit from reduced lung function decline and may be at more risk of infections if treated.

Currently, the evidence for the use of mTOR inhibitors in any aspect of LAM is still emerging but is best for the prevention of loss of lung function. Where possible patients should be considered for appropriate clinical trials if available rather than receiving off label therapy unless essential.

Anti-oestrogen Therapy

Although LAM appears to be an oestrogen dependent disease, to date, no randomised controlled trials of hormonal manipulation have been performed. Observational and retrospective studies have suggested that blocking oestrogen production by oophorectomy, GnRH agonists [64], progesterone [34, 65], or oestrogen receptor binding drugs such as tamoxifen do not affect disease progression in the majority of patients with established disease. Despite this, progesterone and GnRH agonists remain in common use. These drugs are commonly associated with adverse effects: progesterone may cause weight gain and oedema and importantly for patients with LAM has been associated with increased growth of meningioma [66]. GnRH agonist use has been associated with reduced bone density after treatment for LAM [64]. The lack of efficacy of these drugs for LAM is disappointing, the cause of which is unclear. It is possible that LAM cells are less dependent on oestrogen for their growth or survival in established disease. Routine use of anti-oestrogen therapies is not recommended in women with LAM [31]. Recent evidence from breast cancer suggests that inhibition of mTORC1 and oestrogen signalling may inhibit tumour growth more effectively than either agent alone. The use of combined mTOR/oestrogen inhibition would be important to investigate in LAM.

Other Therapies

Studies of the molecular pathology of LAM and the mTOR pathway particularly, have suggested a number of candidate drugs for LAM including the statins [67], modulators of AMP kinase such as metformin, tyrosine kinase inhibitors and the antibiotic and metalloproteinase inhibitor doxycycline [68]. At present there is no clinical trial evidence to support the use of these agents alone or in combination with mTOR inhibitors, however clinical trials of various therapies are currently underway.

Interventions for Advanced Disease

Those with severe disease are likely to develop hypoxaemia, 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 co-morbidities 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 [69]. 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 [70]. 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 [71, 72]. 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 [50, 71]. 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 post operatively. Women with LAM tend to be at risk of low bone density due to chronic lung disease and anti-oestrogen therapies [73]. 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 [50]. Although studies have suggested there is no overall difference in survival between those treated with single or double lung transplant, occasionally overinflation of the native lung can impair the function of the graft after single lung transplantation.

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Pulmonary Alveolar Proteinosis

18

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Definition

Pulmonary alveolar proteinosis (PAP) is a rare disease characterized by alveolar accumulation of surfactant. PAP results of defective surfactant clearance by alveolar macrophages. Diagnosis of PAP is evoked by CT scan and confirmed by staining of bronchoalveolar lavage fluid (BALF) or transbronchial biopsies. Diagnosis rarely requires open lung biopsy. Three main categories of PAP have been individualized depending on the aetiology: autoimmune, secondary and genetic, with some overlap however. Adult forms are mostly autoimmune associated with anti-granulocyte macrophage-colony stimulating factor (GM-CSF) antibodies. When anti-GM-CSF antibodies are absent the main causes are secondary to toxic inhalation or haematological disorders. Genetic PAP is seen especially in children, and radio-clinical presentation depends of the mutated gene.

This chapter summarizes our knowledge of the current pathophysiology of PAP and its three forms.

Pathophysiology

Surfactant

Surfactant consists of a mixture of proteins and lipids (mostly phosphatidylcholine) secreted by type II pneumocytes. The four main surfactant proteins are SP-A, –B, –C and -D and the corresponding genes SFTPA, B, C and D [1]. Surfactant decreases alveolar surface tension and prevents end-expiratory alveolar collapse. Surfactant is cleared by type II pneumocytes and alveolar macrophages. Surfactant is also involved in the alveolar anti-infectious defence.

Abnormalities of Surfactant Clearance

GM-CSF is a key cytokine in PAP pathophysiology. *In vitro*, GM-CSF, a growth factor for granulocytes and monocytes, stimulates differentiation, proliferation and survival of myeloid cells: monocytes, neutrophils and dendritic cells [2, 3]. GM-CSF knock-out (KO) mice show isolated lung lesions reminiscent of PAP seen in humans [3], probably secondary to defective clearance of surfactant by alveolar macrophages.

The human receptor of GM-CSF (CSFR) has two subunits, α and β. The mutations of *CSF2RA* and *CSF2RB*, the coding genes of the α and β subunits, prevent GM-CSF signalling and induce PAP. In PAP secondary to haematological disorders, alveolar macrophages are thought to be quantitatively or functionally unable to clear the surfactant.

Autoimmune PAP specifically shows a high concentration of neutralizing anti-GM-CSF IgG antibodies [4, 5]. Anti-GM-CSF antibodies bind GM-CSF with high affinity, thus blocking its activity [6]. Because of reduced or absent GM-CSF stimulation, alveolar macrophages are unable to clear the surfactant and are also less efficient for anti-infectious defence [7, 8]. Furthermore, neutrophils and lymphocytes are functionally modified, which explains some of the opportunistic infections occurring during PAP [9]. Anti-GM-CSF antibodies are thought to be pathogenic as *in vitro*, anti-GM-CSF antibodies reproduce on myeloid cells from healthy subjects, abnormalities seen on myeloid cells of PAP patients [6], and *in vivo*, perfusion of human anti-GM-CSF antibodies in a non-human primate induced PAP indistinguishable from human PAP [10].

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Autoimmune PAP

Epidemiology

Autoimmune PAP represents about 90 % of all PAP cases [11, 12]. The prevalence varies among countries, from 4 to 40 cases per million, and the incidence is estimated at almost 0.2 cases per million [7, 12]. Altogether more than 600 patients with PAP have been reported so far. Demographics and treatment are similar in the French, Italian, German and Japanese cohorts [13].

Each cohort reveals male predominance with a male to female ratio between 1.25 and 4. Mean age at diagnosis is between 39 and 51 years, but autoimmune PAP may occur from newborns to 72 year olds [14]. About 2/3 of the patients are active or former smokers. Difference of prevalence between men and women may results from smoking as 85 % of the male patients are smokers. Indeed, the sex ratio is 1:1 in non-smoker patients [7, 12].

Clinical Vignette

A 48 year-old smoker man presented dry cough without any remarkable finding on physical examination. The chest radiograph revealed bilateral infiltrates and CT scan showed diffuse ground-glass opacification superimposed on a reticular pattern (Fig. 18.1). The transbronchial lung biopsy showed near completed filling of the alveolar space and terminal bronchioles by periodic acid-Schiff positive acellular surfactant and confirmed the diagnosis of PAP. Anti-GM-CSF was detected in the serum by ELISA. A diagnosis of autoimmune PAP was made. The patient was helped to quit smoking but he still complained of dyspnea. Pulmonary function test showed a DLCO at 60 % of the predicted value. A whole lung lavage was performed with improvement of dyspnea and DLCO. The patient did not receive further therapy until now.

Clinical Presentation

Symptoms are not specific, and almost one-third of patients are asymptomatic [12]. Dyspnea is present in 39 % of cases and, cough, either productive or not, in 21 % [12, 14]. Chest pain, loss of weight, fatigue and fever are rare. Haemoptysis is rare, of mild volume, and should suggest pulmonary infection [14].

Clinical examination results are often normal. Cyanosis or digital clubbing may be present in up to 30 % of cases, and auscultation may reveal crackles [14]. Some studies suggest that older patients might present the most severe form of PAP.

Autoimmune PAP is associated with opportunistic infections in about 5 % of the cases. Specific risk factors are immunosuppressant therapy especially corticosteroids and patients naïves of PAP specific therapy. Presence of anti-GM-CSF antibodies could be associated with a specific risk of *cryptococcal* meningitis [15].

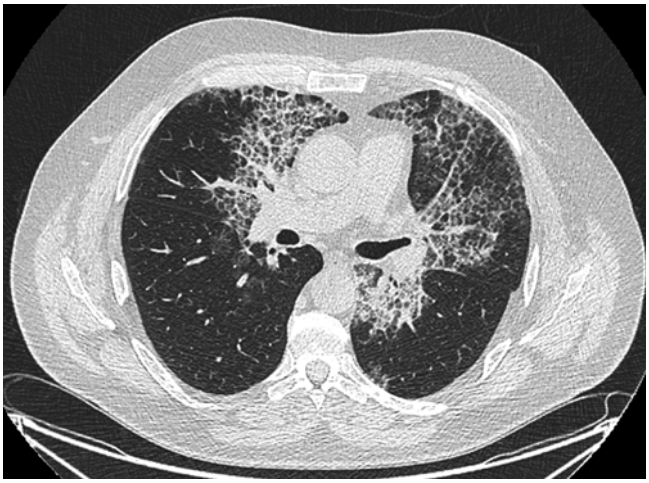

Fig. 18.1 Chest CT scan of a patient with autoimmune PAP. Reticulations are superimposed on ground-glass opacities forming a "crazy paving" pattern with a geographic distribution: juxtaposition of healthy and sick zones

Complementary Exams

Chest X-ray

Chest X-ray reveals symmetric, bilateral, alveolar opacities, without air bronchogram (Fig. 18.1), showing a peri-hilar and basal distribution. Opacities are more rarely asymmetric or with an apical predominance. The pattern resembles acute pulmonary oedema; however, cardiomegaly and pleural effusion are absent [11, 14]. The importance of opacities and symptoms are often discrepant [7].

Chest CT Scan

The pattern observed is highly suggestive of the disease, although not pathognomonic. Main abnormalities are ground-glass opacities, septal reticulations and parenchymal consolidation (Fig. 18.1). Reticulations are frequently superimposed on ground-glass opacities, thus forming a "crazy paving" pattern characteristic of PAP. Opacities have a typically geographic distribution, with juxtaposition of healthy and sick zones. The zonal distribution is usually not specific; however, a lower zone predominance might be present in 22 % of cases [16]. Large focal parenchymal consolidations, pulmonary nodules, and mediastinal adenomegaly are usually absent and should lead to the search for an opportunistic infection [16].

Correlation of histology and radiology findings reveals that ground-glass opacities correspond to a lipoproteinaceous alveolar accumulation. Correlations with reticulation are less unequivocal and could correspond to interstitial disease

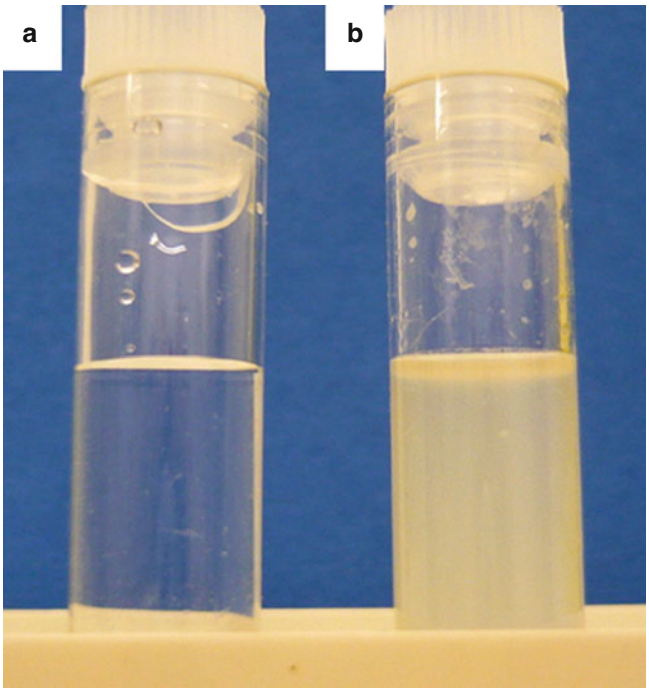

Fig. 18.2 Bronchoalveolar lavage fluid (BALF) with a milky appearance in PAP (**b**) as compared to normal saline (**a**)

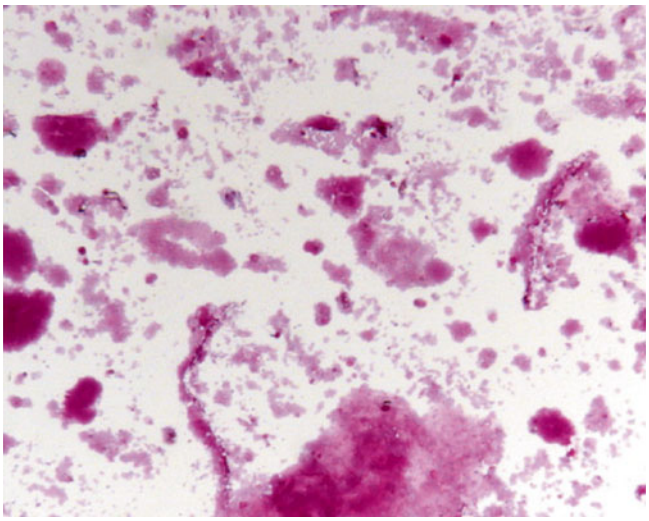

Fig. 18.3 Periodic acid Schiff (PAS) staining of BALF with PAP. Extracellular globular hyaline material homogeneously PAS+, with large, foamy macrophages containing eosinophilic granules

(lipoproteinaceous interstitial accumulation, inflammation or oedema) or lipoproteinaceous alveolar accumulation on the edges of the lobules [17].

A crazy-paving pattern is not specific for PAP and might be associated with lesional or cardiogenic pulmonary oedema, alveolar haemorrhage, pulmonary infection (mycoplasma, pneumocystis), exogenous lipoid pneumonia or bronchioloalveolar carcinoma [17].

The extent of opacities seen on CT scan is associated with impaired pulmonary function on testing [18].

Bronchoalveolar Lavage Fluid

BALF staining is required for the diagnosis of PAP [19]. When performed in a diseased lung area, BALF typically has a milky appearance (Fig. 18.2) but might appear abnormal or normal if performed in a healthy zone, with a weak amount of lipoproteinaceous material.

Cytologic examination and periodic acid Schiff (PAS) staining are mandatory for diagnosis. In one series, BAL cellularity was increased (330,000 cells/ml) with increased proportion of lymphocytes (mean 57 %) [20]. Careful examination reveals large, foamy macrophages containing eosinophilic granules, with extracellular globular hyaline material found homogeneously positive on PAS and negative on Alcian blue staining (Fig. 18.3).

Ultrastructural analysis of BAL fluid is not necessary. It reveals numerous lamellar bodies with a structural resemblance to myelin [7].

Diagnosis of Autoimmune Alveolar Proteinosis

- Positivity of PAS staining of bronchoalveolar lavage fluid (BALF) or transbronchial biopsies
- Positivity of anti GM-CSF antibodies
- In case of alveolar proteinosis diagnosis, without anti GM-CSF antibodies neither haematological disease, consider genetic study

Anti-GM-CSF Antibodies

The dosage of anti-GM-CSF antibodies makes the diagnosis of autoimmune PAP. Anti-GM-CSF antibodies may be detected at low concentration in healthy subjects and could participate to the regulation of myeloid cells [21]. Anti-GM-CSF antibodies of IgG, IgA or IgM isotypes have been detected in sera from patients with acute leukemia, their concentration being associated with disease activity [22]. A concentration greater than 19 µg/ml is specific to autoimmune PAP, and a concentration lower than 10 µg/ml has a good negative predictive value [23]. Conflicting data have been published regarding the concentration, the change of auto-antibody levels and evolution of the disease.

Other Biological Exams

Results of routine biological tests are usually normal. Serum lactate dehydrogenase (LDH) may be increased between two and three times the normal range in half of the cases. Increased LDH may be correlated to the severity of the disease. The serum levels of carcinoembryonic antigen and

KL-6 (Krebs von den lungen-6) could be higher than those for other diffuse interstitial pneumonia and could be associated with disease severity [12]. Initial level of KL-6 correlates with disease progression and to the need of further specific therapy with a positive predicted value of 91 %.

The serum levels of the surfactant proteins SP-A, –B and -D are increased and could be associated with disease severity [12]. However, levels of SP-A and -B do not change with therapy [24]. In contrast, the level of SP-D in non-human primates was helpful in screening PAP development after injection of anti-GM-CSF antibodies. Determining the level of SP-D could help monitor human disease [10].

Although PAP is autoimmune in 90 % of cases, autoimmune PAP is rarely (<2 %) associated with another autoimmune disease [7].

Pulmonary Function Tests and Exercise Capacity

Pulmonary function and exercise capacity tests are important for therapeutic decisions. Spirometry frequently shows a restrictive pattern but may give normal results in 10–30 % of cases. The most constant and significant modifications are hypoxemia and reduced diffusing capacity of the lung for carbon monoxide (DLCO) with increased alveolar–arterial gradient [11, 14]. Therapy may be introduced in patients showing desaturation on the 6-min walking test.

Open-Lung Biopsy

Special attention to BALF, associated with clinical and CT-scan typical presentation, is often sufficient for diagnosis, and open-lung biopsy is not necessary for diagnosis [11]. Transbronchial biopsy may be helpful. In a Japanese cohort of 203 autoimmune PAP, open-lung biopsy was performed for diagnosis in 8 % of the cases and transbronchial biopsy in 42 % of the cases [12].

Prognosis and Evolution

From spontaneous remission to death, disease evolution is unpredictable. Most recently reported cohorts described a spontaneous remission between 5 and 7 %, lower than the 30 % historical reported. Active smoking is a demonstrated factor of aggravation. Since the wide use of therapeutic lavage, 5-year survival with autoimmune PAP is almost 95 % [12].

Evolution to pulmonary fibrosis is possible after a diagnosis of autoimmune PAP. The risk of fibrosis may be higher in patients who describe toxic inhalation. Non-haematological cancers have been reported, but these associations may be a coincidence [12].

Therapy

The standard of care is symptomatic whole-lung lavage. Numerous therapies targeting an enhancement of the surfactant clearance have been investigated, either targeting alveolar macrophages with exogenous GM-CSF or aiming at reducing levels of anti-GM-CSF antibodies with plasmapheresis or rituximab.

Whole-Lung Lavage

Numerous techniques have been reported.

The first method reported, in 1961, is no longer used. Saline was blindly injected through a percutaneous transtracheal endobronchial catheter. The fluid was re-aspirated through the catheter and evacuated by violent coughing [25]. Classical therapeutic BAL is performed under general anaesthesia in an operating room or an intensive care unit. The patient is intubated with a double-lumen endotracheal tube. The patient under curarisation is placed in the dorsal or lateral decubitus position, with the lung being lavaged in the uppermost position. The non-lavaged lung is mechanically ventilated. One liter of warmed (37 °C) saline is injected in the lung. Fluid is then collected by gravity after opening the outflow tube. Manual or mechanical chest percussion might be performed to improve drainage. The process is repeated until the fluid becomes less opaque; 15 L of saline are generally necessary. The patient is extubated a few hours later depending on the clinical evolution. The controlateral lung may be lavaged 24–48 h later [14, 26].

The most frequent complications are low oxygen saturation, convulsions, pneumothorax, pleural effusion, and fever, which may reveal infection. Retrospective data suggest that whole-lung lavage could improve survival [7]. In 85 % of cases, symptomatic, radiographic and functional improvement is obtained after whole-lung lavage: a mean improvement in FEV1 of 0.26 L, in vital capacity of 0.5 L, in DLCO of 4.4 mL/mmHg/min, and in PaO_2 of 20 mmHg, and a mean reduction of alveolar-arterial gradient of 30 mmHg.

According to the centers, between 54 and 90 % of the patients received whole lung lavage. Between 30 and 50 % will need to repeat the whole-lung lavage, on average only one [7]. Almost 10 % of the patients require repeated lavage.

GM-CSF Supplemental Therapy

GM-CSF (Sargramostim®) may be inhaled or subcutaneously administered [27, 28]. Posologies vary from 250 µg to 18 µg/kg/day, fixed or increased dosage, compassionate use or clinical trial.

A meta-analyse had been recently performed with all published data. GM-CSF could be more effective when inhaled, with a response rate at 76.5 % (95 % CI [34.5–95.3]), and a relapse rate of 12.5 % [1.4–64.8]. The response rate of subcutaneous GM-CSF is 48.4 % [33.8–63.3] with a relapse rate of 43.8 [11.8–82.1] after GM-CSF withdrawal. Side effects were considered minor and included injection-site edema, erythema, malaise and shortness of breath.

In the GM-CSF responder group, improvement is slower than after whole-lung lavage. Improvement of PaO_2 could

be of the same magnitude with both therapies, with an increase of 12–19 mmHg with whole-lung lavage [29, 30] and a mean increase of 23 mmHg with GM-CSF therapy in GM-CSF-responder patients, for 9.7 mmHg for all GM-SCF patients [27].

No clinical or biological marker exists to predict response to GM-CSF and to select patients that could benefit from GM-CSF therapy. In one study, factors associated with response to subcutaneous GM-CSF therapy were hypereosinophilia under therapy, longer delay since diagnosis, higher vital capacity, normal serum LDH concentration and increased serum SP-B concentration [27]. Indeed, the initial concentration of anti-GM-CSF antibody and the evolution of concentration under therapy are not associated with response [7, 27, 31]. Low vital capacity at baseline may be associated with relapse and the need for an additional treatment [32].

GM-CSF therapy is now considered an alternative to whole-lung lavage. However, Sargramostim® was withdrawn from several national markets and may require specific authorisation from national health authorities according to each country.

Rituximab and Plasmapheresis

Immunosuppressive therapies, particularly corticosteroids, are not effective in PAP [7] and could increase the risk of pulmonary infection. Theoretically, plasmapheresis should be effective to decrease the concentration of anti-GM-CSF antibodies and improve the disease as in Goodpasture disease [33]. Only two cases have been reported in the literature: a decrease of anti-GM-CSF antibodies was measured in both cases, and one patient showed a striking improvement and the other a mild improvement [34, 35].

Rituximab, a monoclonal antibody directed against the CD20 antigen of B lymphocytes, could ameliorate PAP by decreasing anti-GM-CSF antibody concentration. Two cases have been reported in the literature of rituximab efficacy [36, 37]. A prospective monocentric open-label study evidenced an improvement in seven of the nine treated patients with rituximab associated with a decrease of serum anti-GM-CSF antibody concentration [38]. Most patients received 1,000 mg of Rituximab, days 1 and 15. Mean increase of PaO_2 was 12 mmHg 3 months after therapy. Rituximab was well tolerated in all patients.

Although the exact place of these treatments is not well defined yet, rituximab therapy could be an alternative for whole-lung lavage resistant disease.

Secondary PAP

Secondary PAP includes PAP secondary to immune deficiency, cancer and particularly haematological diseases, and secondary to toxic inhalation.

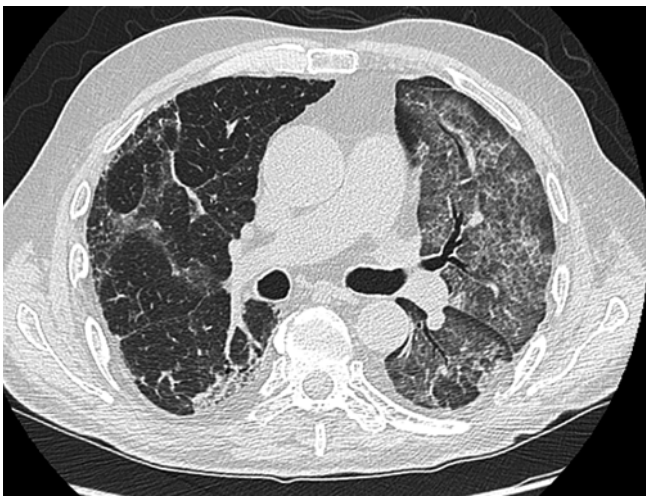

Fig. 18.4 Chest CT of a patient that developed PAP after lung transplantation CT shows ground-glass opacities and reticulations. PAP resolved with modification of immunosuppressive therapy

Immune Deficiency

PAP has been rarely associated with immune deficiency, including severe combined immunodeficiency, agammaglobulinemia [39], or organ transplantation (Fig. 18.4) [7]. A few cases of connective tissue diseases have been reported: dermatomyositis [40], rheumatoid arthritis [41], and Behcet's disease [42, 43]. The, recently described, MonoMAC syndrome include monocytopenia, mycobacterial diseases and frequent PAP [44]. MonoMAC syndrome is associated with *GATA2* mutations and will be described further.

Cancer

The association of PAP and haematological disorders is well established, mostly myelodysplastic syndromes (8–74 % of the cases) and acute myeloid leukaemia (5–21 %) [43]. Some cytogenetic abnormality such as trisomy 8 could be more frequently associated with PAP. PAP could explain up to 10 % of pulmonary manifestations during these diseases [45]. Less frequently, PAP has been associated with acute lymphoid leukaemia [46], lymphoma [47], and myeloma [48]. In haematological diseases, alveolar macrophages could be numerically or functionally unable to clear the surfactant.

PAP is generally diagnosed during the evolution of haematological disease and may occur in the absence of detectable tumour after bone marrow transplantation [49]. The diagnosis of PAP and haematological disease may occur simultaneously; in that case, the diagnosis of the haematological disease is generally easy [43, 50].

The classical presentation is respiratory insufficiency with fever in 24 % of the cases, particularly in patients with

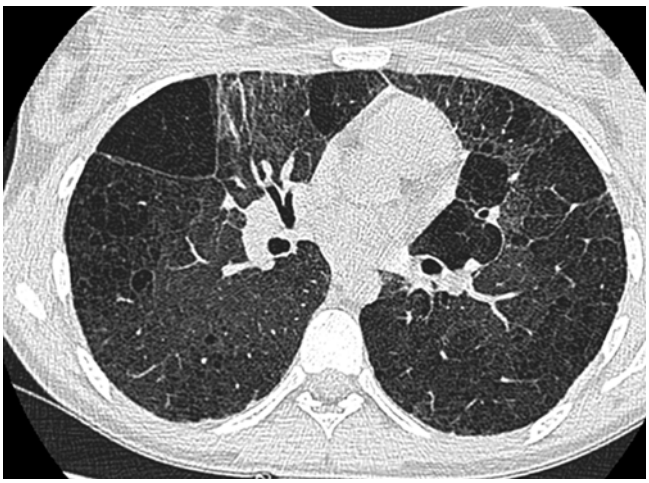

Fig. 18.5 Chest CT scan of a patient with interstitial lung disease associated with *ABCA3* mutation PAP. CT scan shows diffuse ground-glass opacities and lung cysts

prolonged neutropenia secondary to chemotherapy [45]. However 20 % of the patients may be asymptomatic at the diagnosis.

Chest X-ray shows diffuse interstitial opacities [45]. Chest CT scan may show the typical crazy paving pattern. CT scan may also be less suggestive by showing ground-glass opacities mainly in the lower zone without subpleural sparing or consolidations (Fig. 18.5) [47, 51]. Fiberoptic bronchoscopy is diagnostic. Interestingly, BALF analysis may reveal PAP and an associated opportunistic infection. Pulmonary infection with *Nocardia*, *Pneumocystis*, *Acinetobacter*, *Aspergillus*, *Cladosporium*, or *Mycobacerium tuberculosis* or non-tuberculosis Mycobacteria have been associated with PAP [47, 52]. Positive PAS staining of intra- and extracellular material is sufficient for the diagnosis of PAP and may negate a lung biopsy or autopsy [45, 53]. In a retrospective study of 40 cases, the diagnosis was made by BALF analysis in 21 cases, by transbronchial biopsies in 9 cases and by surgery in 10 cases.

The prognosis is poor and the median time of survival of less than 20 months. In a retrospective study of 35 patients and in a review of 44 patients, the causes of deaths were: haematological disease (33 %), infection (29 %), and respiratory insufficiency (25 %).

Less than 20 % of patients who benefited from whole-lung lavage showed improvement [54]. Haematological therapy alone, chemotherapy and/or bone-marrow transplantation, can cure PAP, particularly in cases of acute leukaemia [55, 56].

PAP may be associated with non-haematological cancers, most frequently lung cancers (squamous cell cancer (N=2), adenocarcinoma (N=2)) and more rarely, mesothelioma, melanoma with lung metastasis and glioblastoma (N=1 each) [57]. For at least one of these cases, anti-GM-CSF antibodies were detected. This association could be a coincidence in view of the frequency of lung cancer.

Inhalation of Toxic Particles

Numerous case reports or short series describe PAP after inhalation of mineral particles (silica, talc, cement, kaolin), metal particles (aluminium, titanium, indium), or more rarely organic particles (fibres of cellulose) [7, 11, 58]. PAP may occur after massive inhalation of silica and is then called acute silicoproteinosis [7]. Clinical presentation is close to that of autoimmune PAP.

Numerous animal models demonstrated the development of PAP after inhalation of nickel, silica, titanium, quartz, fibreglass, indium or aluminium powder [11, 59, 60]. In the French series reported by Briens et al., in 2002, 39 % of patients reported notable professional exposure to particles [14]. Furthermore, in the Japanese cohort of 248 patients with autoimmune PAP, 23 % were considered exposed to toxic inhalation [12]. However anti-GM-CSF antibodies were detected in a patient with PAP secondary to indium inhalation [58]. This suggests that some of the secondary PAP may be associated with anti-GM-CSF antibodies and that toxic inhalation could be a trigger for an autoimmune disease [61].

Clinical presentation is close to that of the autoimmune PAP, but evolution may be more severe. In a Japanese series of 88 patients, 15 were dead. Causes of death were: respiratory insufficiency including pulmonary fibrosis (n=8), cancers (n=3), infections (n=2); Median survival was 17.2 years. Persistent toxic inhalation was associated with a worse prognosis [62].

Genetic PAP

Genetic PAP could be divided in two groups:

- Mutations that involved the production of surfactant *SFTPB*, *SFTPC*, ATP-binding cassette 3 (*ABCA3*) and NK2 homeobox 1(*NKX2-1*).
- Mutations that involved the macrophage and the degradation of surfactant, GM-CSF receptor, α or β subunit, mutations of *GATA2* as well as lysurinic protein intolerance.

Moreover, a large kindred of 32 patients with PAP originated from La Reunion island has been recently described [63]. The diseases occurred in the first 6 months of life with a 59 %, 5 years mortality. Associated liver diseases were frequent. To date, the very probable mutated gene has not been described.

Mutations of *SFTPB*, *SFTPC*, *ABCA3* and *NKX2-1*

The term of PAP has been widely used in patients with surfactant mutation associated disorders [64]. Indeed, both entities share similar clinical characteristics which probably explain the confusion [65]. The radiological and the histological presentation are nonetheless different. In both

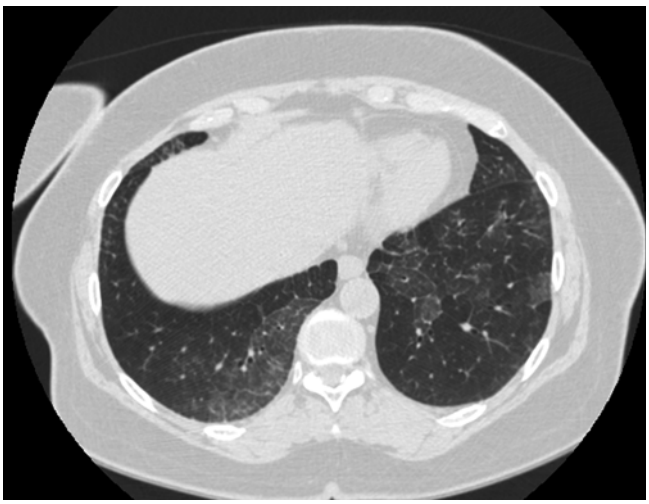

Fig. 18.6 Chest CT scan of a patient with PAP secondary to myelodysplastic syndrome. CT shows ground-glass opacities and reticulations mainly in the lower zone with patchy, slightly peripheral distribution

children and adult, diffuse ground-glass opacities and lung cysts are the common radiological features observed in surfactant protein disorders whereas septal reticulations, and parenchymal consolidation usually described in autoimmune PAP are less frequent (Fig. 18.6) [66, 67]. The histopathologic findings in infants with mutations in the *SFTPB*, *SFTPC*, *ABCA3* or *NKX2*.1 genes are remarkably similar, demonstrating varying degrees of interstitial thickening, a remodelling of the alveolar epithelium with type II cell hyperplasia, as well as alveolar accumulation of eosinophilic, lipoproteinaceous, granular material [66–69].

Along with the preventive measures, and in the absence of studies, the choice of azithromycin and/or hydroxychloroquine in association with steroid remains highly dependent on the habits and experiences of the different centres. Lung transplantation may be considered [66, 67, 70, 71].

Genetic Defect in GM-CSF Receptor

GM-CSF receptor is composed of the binding α chain (CD116), coded by *CSF2RA*, and the common β chain (CD131), coded by *CSF2RB*, which is also shared by IL-3 and IL-5 receptors.

Mutations of *CSF2RA* have been described only in children, and a series of eight patients from 1.5 to 9 years was recently reported [72]. Mutations of *CSF2RA* could correspond to 6 % of all PAP [72]. *CSF2RA* is located on X and Y chromosomes. The transmission is autosomal recessive. Very recently the mutation was described in a 3 year patient with PAP after a complex inactivation of the naïve gene in the other X chromosome [73]. Some mutations have varying and incomplete penetrance, and disease was found in three asymptomatic children between 5 and 8 years after the diagnosis of a familial index case [74].

Except for a lower age at disease onset, patients with mutation of *CSF2RA* present PAP close to autoimmune PAP. Indeed, unlike mutations of surfactant proteins, interstitial cell infiltration is absent. However, alveolar and serum concentration of GM-CSF is increased, and anti-GM-CSF antibodies are absent.

Mutation of *CSF2RB* was suggested in three patients presenting neonatal PAP and confirmed in a 36 years woman and in 9 years girl [75–77]. Both showed disease close to autoimmune PAP without detectable anti-GM-CSF antibodies but with high concentration of GM-CSF [77].

Whole-lung lavage may be effective [78]. GM-CSF therapy does not seem to be effective [75, 78, 79].

Lysinuric Protein Intolerance

Lysinuric protein intolerance is an autosomal-recessive disease caused by mutation of *SLC7A7* contributing to defective transport of cationic amino acid at the membrane of epithelial cells in the intestine and kidney. In Japan, the estimated prevalence is 1/57,000 births. The clinical presentation is characterized by 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 (arginine, lysine, ornithine) in the urine, particularly after protein ingestion, and/or mutation of *SLC7A7* [80, 81]. The treatment is based on a low protein diet and oral supplementation with citrulline.

PAP is frequently present. Indeed, expression of *SLC7A7* is a target of GM-CSF that could explain the reduced activities of alveolar macrophages [82].

Nebulised GM-CSF therapy seem to be effective [82]. However, PAP may lead to death and relapse after lung transplantation [83, 84].

Monomac Syndrome

MonoMAC syndrome is a recent described immune deficiency. It is characterized by disseminated mycobacterial infection, particularly with *Mycobacterium avium complex*, opportunistic fungal infection, papillomavirus infections. PAP may be present in 18 % of the cases [85].

In the blood, monocytes, NK- and B-cells are not detected. Patients frequently develop during evolution myelodysplasia, acute leukemia or chronic myelomonocytic leukemia. The syndrome is associated with *GATA2* mutations. *GATA2* regulates phagocytosis by the macrophage and may explain PAP.

At least two patients with severe PAP were improved by allogenic hematopoietic stem cell transplantation [44].

Telomerase Mutation Complex

Telomerase is the enzyme that catalyses the addition of repetitive DNA sequences to telomeres, the structures that protect chromosomes from erosion. Telomerase activity requires a complex of proteins and RNA, such as telomerase reverse transcriptase (TERT). Mutations in the telomerase complex may lead to pulmonary fibrosis, cirrhosis, bone marrow failure or cutaneous diseases.

A 35 years patient with initial diagnosis of PAP and evolution to lung fibrosis associated with *TERT* mutation had been recently described [86]. The pathophysiology of PAP in this context is matter of speculation.

The patient initially responded to GM-CSF, but not to whole lung lavage. He died of lung fibrosis at the age of 46 years.

Conclusions

PAP are rare diseases, secondary to alveolar macrophages dysfunction. Diagnosis is generally easy when evoked. Numerous therapies are actually available in autoimmune PAP, but whole lung lavage remains the first line therapy. Smoking and toxic inhalation must be avoided. Treatment of secondary forms of PAP is based on etiological treatment such as allogenic stem cell transplantation.

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Exogenous Lipoid Pneumonia

19

Anne Gondouin and Jean-Charles Dalphin

Exogenous lipoid pneumonia (ELP) results from the presence of various fatty substances, usually aspired or inhaled, in the lung parenchyma.

ELP is the usual terminology used for this condition, but is not entirely adequate to all cases described. Indeed, many of these cases are related to mineral oils, which are not lipids, but saturated hydrocarbons. However, this terminology will be conserved throughout this chapter.

Endogenous lipoid pneumonia occurs in different settings such as chronic bronchial obstruction, chronic pulmonary infection, pulmonary alveolar proteinosis or fat storage diseases. The latter will not be taken into account in this chapter.

Introduction

Exogenous lipoid pneumonia was initially described by Laughlen [1] in 1925 in patients with pneumonia caused by oily rhinopharyngeal drugs. Two large studies were published in the next 10 years. In 1928, Pinkerton [2] studied the effects in the lung parenchyma of vegetal, animal and mineral oils introduced through the upper airways. In 1937, Ikeda [3] reviewed 106 cases published in the literature and concluded that the lesions observed in humans and in animals were similar. Further large series were subsequently published: 411 cases reported by Kaplan [4] in 1941, 264 by Sweeney [5] in 1943, and 131 by Sodeman and Stuart [6] in 1946. In 1951, Volk et al. [7] carried out systematic sputum examinations in 389 chronically ill patients and found 57 of them to have ELP. In 1955, Greenridge and Tuttle [8] conducted an analysis of 600 consecutive autopsies performed over 7 years, and identified 40 cases of ELP and in 1976, Rouffy et al. [9] reported a series of 81.

Other authors have highlighted particular patterns of ELP: in 1950, Proudfit et al. [10] mentioned the first occupational case, in an employee who oiled the drawers of a cash register; in 1943, Wood [11] published a case of an ELP associated with bronchial cancer; in 1967, Guest et al. [12] reported ELP associated with superinfection by atypical mycobacteria, which was subsequently described repeatedly.

Epidemiology

ELP is a highly uncommon condition and its precise frequency is difficult to determine. Autopsy series have reported a prevalence of 1–2.5 % [8]. This prevalence has been reported to be higher in some targeted populations: 14.6 % in elderly patients hospitalized with chronic diseases and known risk factors such as bed confinement or chronic constipation [7] and 6.3 % in hospitalized mentally retarded patients [13].

ELP is not associated with gender. Conversely, a high prevalence has been associated with childhood and old age. In the past, ELP was not uncommon in children when the use of cod-liver oil or mineral oils (oil-based nose drops for chronic rhinoparyngeal diseases) was widespread; a prevalence of 6.9 % was reported in an autopsy series published in 1935 [14]. In 1942, The Council on Pharmacy and Chemistry issued a warning on this disease [15] and numerous oil-based medications were removed from the market. Although this lead to a decrease in the frequency of ELP in children, traditional oil-based medicines are still used to treat various diseases in some countries: in South India, for example, the local custom of giving oil baths to children or of cleansing the mouth, throat, and nose with oil has not disappeared, and some cases of ELP are still reported in children [16].

Nowadays, ELP is essentially an adult condition, with a frequency that increases with age due to predisposing factors such as neurological diseases, bed confinement and gastro-oesophageal reflux…

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The duration of exposure to oily substances related to ELP is generally long, from months to years. It may, however, occur after a brief, even single exposure such as accidental poisoning at home in children or "fire-eater's" pneumonia in adults.

Pathophysiology and Histopathology

The pulmonary toxicity of oily products depends on their composition, especially on the rate of free fatty acids, which are hydrolyzed by lung lipases into new free fatty acids. These newly metabolized free fatty acids are toxic for the lung parenchyma.

Vegetal oils have a low percentage of free fatty acids, are slowly hydrolyzed in humans and thus are either non toxic or only slightly so. They do not cause inflammatory lesions and are eliminated after a few weeks.

Conversely, animal oils are highly toxic and trigger a severe inflammatory reaction in the lung, with focal edema and intra-alveolar hemorrhage. They can cause necrotico-hemorragic pneumonia, which may be fatal.

Mineral oils – a mixture of inert, long-chain, saturated hydrocarbons obtained from petroleum – have an intermediate toxicity and cause mild inflammation. They inhibit the cough reflex and ciliary motility, thus facilitating inhalation, even if predisposing factors are not present. There is no acute initial reaction after inhalation. Chronologically, oil is first present as free oil droplets in the air-cells. Lipid-laden vacuoles then appear inside macrophages located in the air-cells, alveolar walls, interstitium, possibly in the satellite lymph nodes and even in the general circulation. The presence in the systemic circulation of lipid-laden macrophages can explain the presence of oily granulomas, which have sometimes been reported in the kidneys, liver or spleen. Advanced lesions show larger lipid vacuoles surrounded by inflammatory infiltrates that can form giant-cell granulomas. Finally, fibrosis can appear in the lung, either exclusively interstitial, or mutilating with a disorganization of the pulmonary architecture. Even in the latter case, fatty deposits are still recognizable. Fibrosing lesions can mimic tumors as they look like nodules macroscopically. They are firm or hard, whitish-yellow and they release a fatty liquid.

Etiology and Predisposing Factors

Numerous oily products have been identified in ELP [17, 18].

- Vegetal oils are used in drugs, or are used for feeding or local customs. Their toxicity depends on the composition and circumstances of inhalation (aspiration during swallowing or vomiting): olive oil, sesame oil, peanut oil, wheat germ oil, cotton seed oil, castor oil, plant seed oil, gingelly oil (used in an Indian custom of giving oil baths to children and cleansing their mouth, throat and nose with oil) and chaulmoogra oil (to treat leprosy). Oil products are also used for diagnostic examination: lipiodol contains poppy seed oil and was considered initially as non toxic. However, persistent radiological images have, on occasion, been reported and interpreted as foci of lipoid pneumonia [19]. Nowadays hydrosoluble products are preferred.
- Animal oils are essentially used for food: cod-liver oil, halibut-liver oil, shark-liver oil (also called squalene), ghee oil, axonge fat, egg yolk fat, oils derived from dairy products. One case in the literature describes an engineer who burned bacon fat to test a fire-extinguisher used in catering [20].
- Mineral oils are the ones most frequently encountered in ELP. The most common are paraffin and vaseline, used in several medicinal products for rhinopharyngeal diseases or constipation. They are also used to lubricate tracheotomy tubes, which results in ELP often thought at first to be a metastasis of the cancer that had justified the tracheotomy [21].

  Mineral oils are also found responsible in occupational cases: lubricants and cutting fluids in fluid or spray form, for turning, milling and grinding operations [22, 23], paraffine for protecting car bodies [24], paraffining of cardboard tableware for domestic use [25], airline pilot masks coated with vaseline, endolaryngeous instillations by professional voice users (singers or teachers using vegetal oils replaced with paraffin in the post-war period due to shortage of supply) [26].

  The literature also informs about numerous anecdotal cases with unusual oils or circumstances of administration: smoking blackfat tobacco, a Kentucky product coated with oil and petroleum jelly to flavor and moisturize the leaf – responsible for a diffuse form of ELP; paraffin oil used for frying food; paraffin used as a non-caloric oil by an anorexic girl; ruptured oleothorax (method of filling the pleura in the treatment of tuberculosis); mineral oil embolization in an infant treated for Hirschsprung's disease; excessive use of lip balm; overuse of dusting spray; leather-care spray; spray for rheumatic pains; subcutaneous injections of silicone in transsexual men; diffuse lipoid pneumonia in a commercial abalone diver due to inhalation of aerosolized mineral oil contained in the unfiltered air generated from his surface air compressor; olive oil injected into the scrotum to enhance the genitals; suicide attempted by immersion in mineral oil; chronic use of primrose oil for the treatment of premenstrual tension syndrome and anxiety; aspiration of diesel fuel while siphoning it; accidental aspiration of lamp oil; inhalation of crack cocaine mixed with petroleum jelly; daily use of petroleum jelly for plugging ears before swimming or showering in a patient with tympanic membrane perforation; facial application of

petrolatum for erythrodermic psoriasis; inhalation of insecticide; inhalation of water-proofing spray; suicide attempted by intravenous injection of lamp oil; ELP related to smoking weed oil; near drowning in a river contaminated with kerosene; aerosol therapy with gomenol or amphotericin B; association of parenteral feeding and gastro-oesophageal reflux; ELP in patients with a digestive form of Chagas disease who suffer from constipation due to a megacolon and have a tendency to aspirate due to a megaoesophagus.

Numerous factors can increase the risk of ELP: the use of oily substances at bedtime, neurological conditions that result in swallowing dysfunction or affect the cough reflex (coma, encephalopathy, cerebral vascular accidents), anatomic or functional abnormalities of upper aerodigestive tracts responsible swallowing dysfunction or regurgitation (cleft palate, ENT carcinoma, oesotracheal fistula, Zenker diverticulum, megaoesophagus, achalasia, hiatal hernia, gastro-oesophageal reflux) and finally, psychiatric diseases in which laxative substances are frequently used.

Oily products are given to children for constipation or to facilitate digestion (for example, cod-liver oil), but they often object vigourously to taking the oil, which precipitates swallowing dysfunction and aspiration, hence the possibility of lipoid pneumonia.

ELP can also occur in healthy individuals: oil, especially mineral oil, is easily aspirated because of its cough reflex and ciliary motility inhibition properties.

Clinical Manifestations

Clinical Vignette

A 36-year-old non smoking woman was admitted to the hospital while her mother, who was in charge of her, was hospitalized. In fact, this patient was diagnosed as having severe multiple sclerosis with quadriplegia that left her with slight motricity in the left upper limb, cerebellar syndrome, and impairment of several cranial pairs responsible among other things for swallowing dysfunction. Eating was limited to semi-liquid food in a seated position.

Other than neurologic lesions, she was asymptomatic. However, the right basal region was dull on percussion and hypoventilating on auscultation. Chest X-ray showed airspace consolidations in the middle and lower right lobes, and in the lower left lobe.

Biological examination revealed only an inflammatory syndrome with mild anemia, elevation of erythrocyte sedimentation rate (67 mm), and elevation of fibrinogen (6.4 g/l). C-reactive protein was normal.

The arterial blood gas analysis (breathing room air) showed hypoxemia ($PaO_2 = 8.6$ kPa) and hypocapnia ($PaCO_2 = 4.3$ kPa).

All bacteriologic analyses were negative and imaging features did not change with antibiotic treatment.

CT scan of the chest confirmed airspace consolidations in the middle and lower right lobes, and the lower left lobe, which were unusually hypodense (Fig. 19.9).

Bronchoscopic examination showed no endobronchial lesion and bronchoalveolar lavage contained many macrophages with cytoplasmic vacuoles, which were often voluminous and stained with fat stains.

It was then that the patient's use of paraffin oil to treat chronic constipation was identified. The inhalation of paraffin was favored by bed confinement and swallowing dysfunction.

This treatment was discontinued and no further treatment was proposed because of her good clinical tolerance of ELP. The patient was seen 3 months after hospitalization and was still asymptomatic with unchanged clinical and radiological examination. She was then lost to follow-up.

Oil intoxication is usually chronic over a long period of time. In this case, ELP is often asymptomatic and identified only incidentally on radiological imaging. When present, symptoms are usually mild and non specific: cough, moderate exercise dyspnea or low-grade fever. The patent forms are also possible with cough, sputum, dyspnea, hemoptysis, chest pain and general signs such as fever or weight loss [18, 27]. Finger clubbing has been reported, though rarely. Auscultation of the lungs is normal or can reveal crackles or rhonchi.

The clinical presentation may, more rarely, be serious at once, either in the form of acute respiratory failure, especially in isolated, accidental cases of aspiration or inhalation, or in the form of chronic respiratory failure with cor pulmonale related to advanced lesions with fibrosis.

An example of accidental inhalation often related in the literature is fire-eater's pneumonia [28], which occurs in performers who swallow the petroleum derivative kerdane, then, after flame-blowing, take a deep breath and inhale the kerdane that remains in the mouth. The clinical and radiographic profiles here differ from those in chronic lipoid pneumonia: symptoms occur within the first 12 h after aspiration and are acute, with chest pain, cough, dyspnea fever and hemoptysis. Tomodensitometry examination shows bilateral consolidations, often associated with cavitary lesions (pneumatoceles). The evolution is favorable in most cases; symptoms disappear within 2–3 weeks and radiological resolution of the pneumatoceles within 2–12 months. Complications such as bronchopleural fistula and pyopneumothorax occasionally occur.

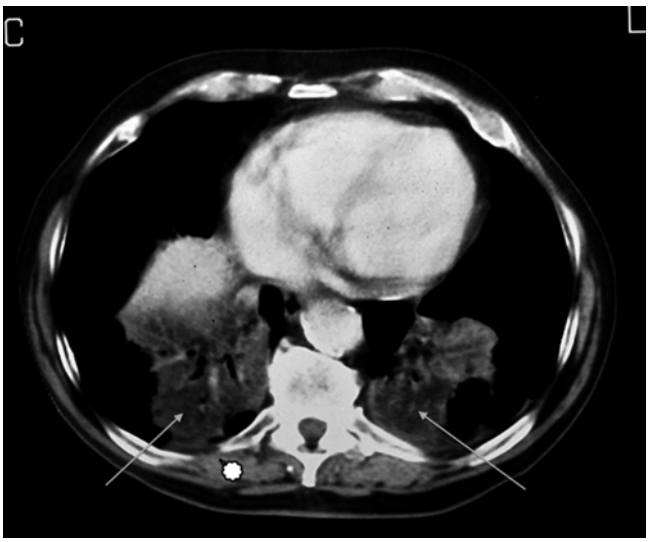

Fig. 19.1 CT scan (mediastinal window). Hypodense bilateral condensations in the lower lobes (*arrows*). The low density can be measured (not available measure for this section) or evaluated relative to muscular density (*star*)

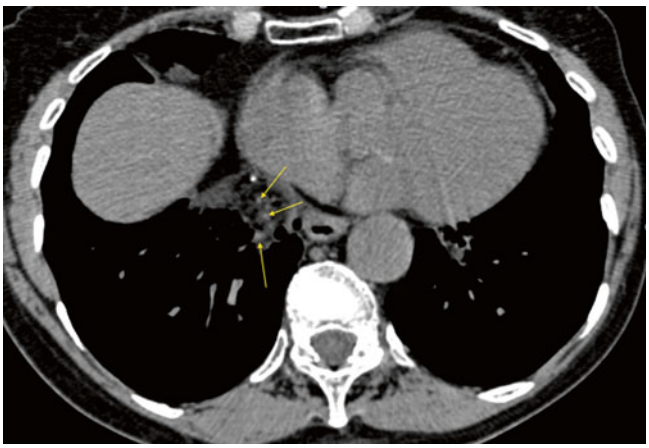

Fig. 19.2 CT scan (mediastinal window), without contrast injection. "Angiogram sign": several cross-sectioned angiograms within the hypodense consolidation (*arrows*)

Diagnosis

Radiological Examinations

Chest x-ray often shows a localized airspace consolidation, either alveolar, which corresponds to an early form of the disease, or irregular mass-like lesion called "paraffinoma", which is the advanced fibrosing lesion. These lesions are most commonly observed in the middle or lower right lobes, but the other lobes may also be affected.

Occasionally, these opacities are multiple, uni- or bilateral and, in rare cases, may have a cavitary aspect or be associated with pleural reaction or mediastinal lymphadenopathies.

ELP can also appear as a diffuse interstitial pattern, reported in cases in which the aeticological agent is inhaled in the form of sprayed oily particles, especially in the professional etiologies.

Rarely, the radiological manifestations include pneumatoceles, pneumomediastinum, pneumothorax, and/or pleural effusion, especially in the acute forms, as in fire-eater's pneumonia.

We can also report the possibility of normal thoracic imaging, despite the presence of oil in the lungs shown by bronchoalveolar lavage. This is observed during systematic screening by workers who are exposed to sprayed oils.

Computed tomography [29, 30] helps to diagnose ELP by revealing areas of fat attenuation within the consolidative opacities and nodules (Fig. 19.1). The density of pure mineral oils ranges between −150 and −60 HU (Hounsfield Units). The densities measured in ELP are somewhat higher because of the surimposed inflammatory lesions. If the density cannot be measured, it can be evaluated relative to muscular density, or can be asserted by the "angiogram sign", which consists of visualization of normally branching pulmonary vessels within the hypodense consolidations, in the absence of contrast injection (Fig. 19.2) [27]. Imaging features may vary considerably: more or less dense ground glass opacities (Fig. 19.3a, b), crazy-paving pattern [31, 32], air-space nodules or consolidations. Fibrosis lesions are visible in the advanced stage of the disease, with interlobular septal thickening and architectural distorsion (Fig. 19.4).

One characteristic feature is the "paraffinoma", which is a mass-like, irregular, spiculated lesion within areas of fat attenuation (Fig. 19.5a, b)

If the lung injury is declivous, images will have a "sandwich appearance" that some authors [27] consider as characteristic, with a subfissural zone of healthy lung between two pathological zones (Fig. 19.6a, b). The declivity of these lesions can sometimes be highlighted with procubitus sections.

Finally, the advent of tomodensitometry and its use in recent series have allowed to show ELP lesions to be far more diffuse than initially described, with frequent bilateral, plurilobar involvement.

Magnetic resonance imaging is seldom used. Findings are a high signal intensity on T1-weighted images and a slow decrease of signal on T2-weighted images [30].

PET scan shows lesions that can increase the uptake of 18F-FDG because of the inflammatory component and thus be misinterpreted as a malignancy [33].

Bronchoalveolar Lavage

The appearance of the fluid retrieved by bronchoalveolar lavage (BAL) suggests a diagnosis of ELP when it shows an oily component on the surface.

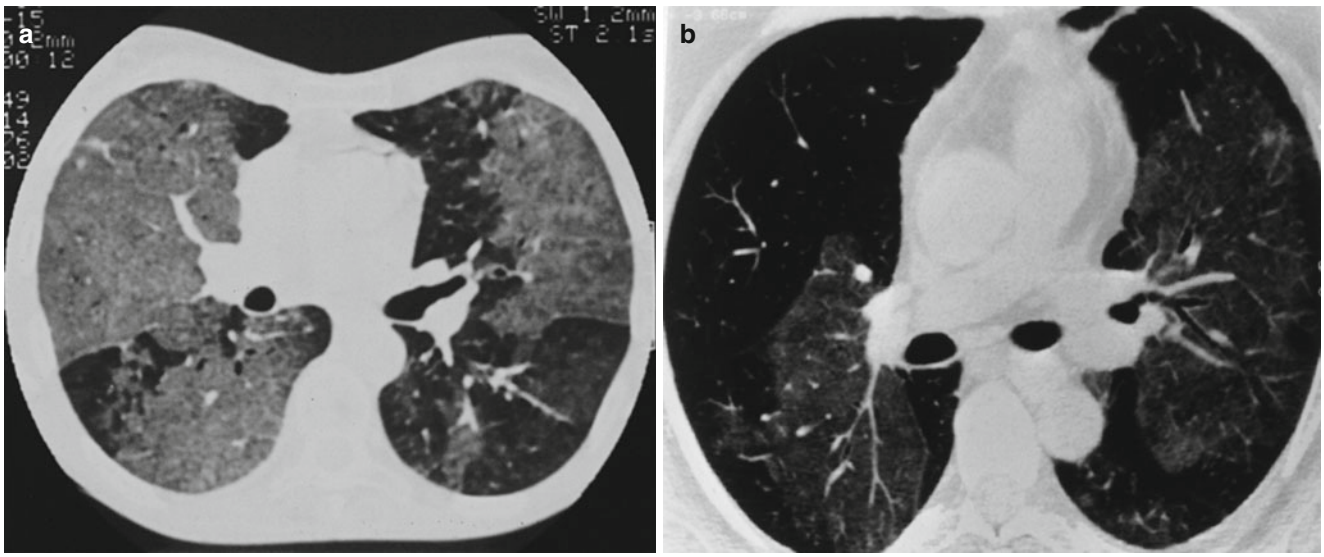

Fig. 19.3 (**a**, **b**) High-resolution CT scan (lung window). Bilateral, dense or less dense ground-glass opacities

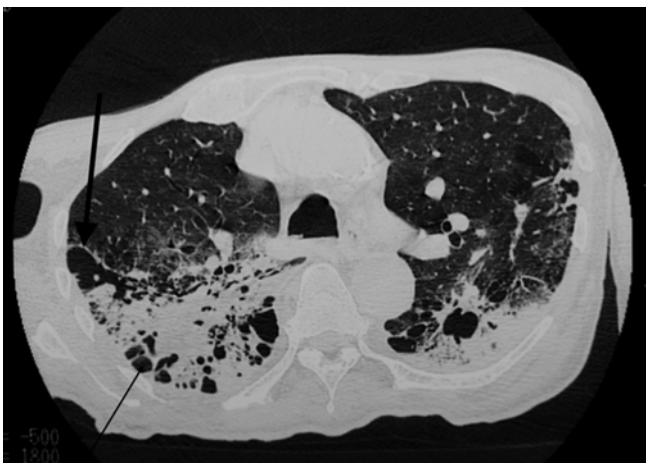

Fig. 19.4 High-resolution CT scan (lung window). Parenchymal condensation of the lower lobes, with signs of fibrosis: kystic images (*thin arrow*), architectural distorsion with scissural deformation (*thick arrow*)

Cytological analysis reveals a normal or high mean cellularity with various cytological profiles: macrophage alveolitis, lymphocytic alveolitis or neutrophilic alveolitis; the latter can suggest a fibrosing course in the absence of infection. Alveolitis can also be mixed and no cytological profile is, therefore, more particularly suggestive of ELP [27].

Optical microscopy analysis after standard stains show lipid-laden macrophages that contain optically empty vacuoles with a negative Periodic acid-Schiff and negative Blue Alcian content. The fat stains using (Red Soudan, Black Soudan) allow to color these vacuoles or to show free oily droplets in BAL (Fig. 19.7).

The fats can be characterized by chemical analysis – either chromatography or infrared spectroscopy – which will allow accurate identification of the oil and prove its exogenous origin. However, these techniques are not commonly used. They are particularly useful if either intoxication by oil or occupational origin cannot be proven.

Diagnosis of Exogenous Lipoid Pneumonia

- Frequently fortuitous discovery or non specific clinical presentation (cough, sputum, mild dyspnea)
- Compatible radiological aspect: unique or multiple, uni- or bilateral opacities, which can contain areas of fat attenuation with a low density range between −75 and −30 Hounsfield units. Possible diffuse interstitial lung disease (occasional "crazy-paving") pattern.
- Detection of intrapulmonary fats, either in bronchoalveolar lavage or specimens for histological examination: presence of substances stained with specific fat stains (Red or Black Soudan), in free form or in form of vacuoles in macrophages cytoplasm (lipophages)
- Evidence of exogenous oily intoxication
- Oil identification if necessary (exogenous intoxication not found, or professional disease) by biochemical analysis: chromatography or infrared spectroscopy.

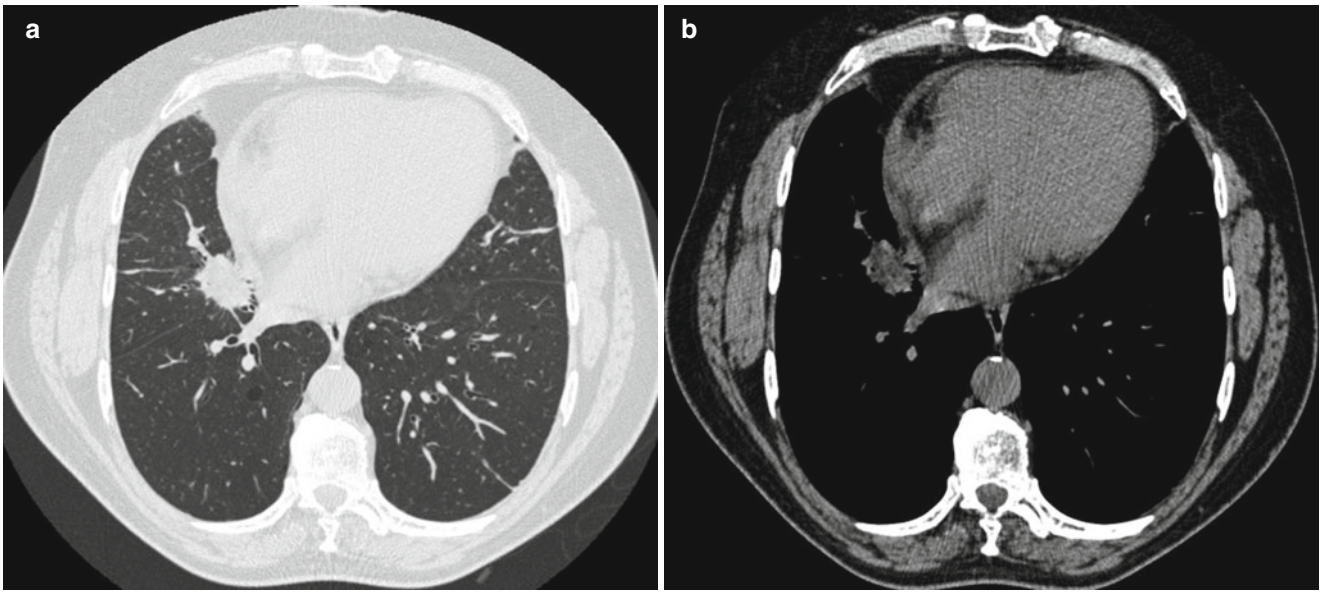

Fig. 19.5 (**a**) High-resolution CT scan (lung window). Paraffinoma: mass-like, irregular, speculated lesion. (**b**) CT scan (mediastinal window obtained at the same level). Areas of fat attenuation within the lesion

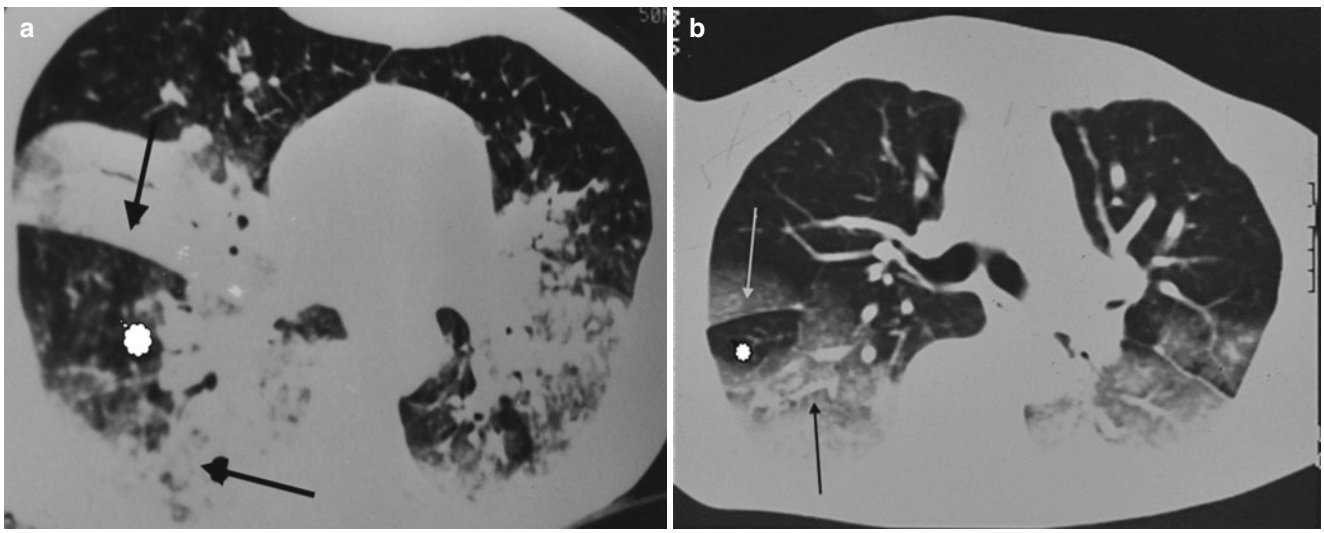

Fig. 19.6 (**a**, **b**) High-resolution CT scan (lung window). Declivity of the lesions, responsible for the "sandwich appearance", with a subfissural zone of healthy lung (*star*) between two pathological zones (*arrows*)

Histopathology

The presence of oily substances can also be confirmed by histologic analysis, with specimens obtained by transbronchial biopsy, percutaneous fine-needle aspiration biopsy, thoracoscopic lung biopsy, open lung biopsy or operative specimen. The techniques used are the same as for BAL: chronic ELP is characterized by the presence of lipid-laden macrophages that fill and distend the alveoli and interstitium, where they may be associated with accumulation of

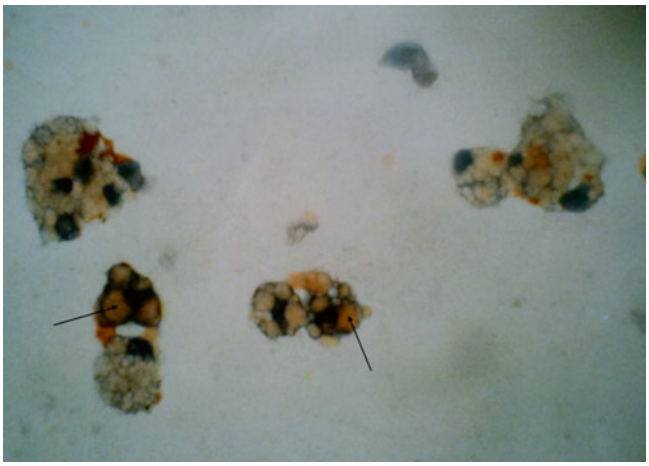

Fig. 19.7 Bronchoalveoloar lavage. Oil red O stain ×40. Intramacrophagic vacuoles (*arrows*) stained in orange

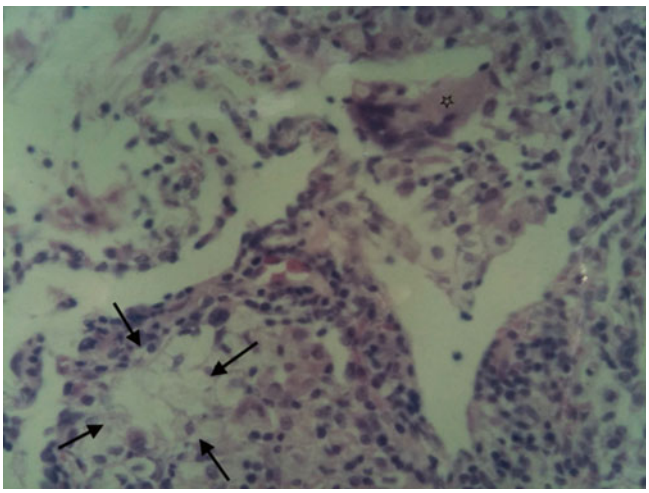

Fig. 19.8 Open lung biopsy. Hematoxylin and Eosin stain ×40. Lipohagic granuloma (*arrows*). Resorptive giant-cell (*star*)

lipid material, inflammatory cellular infiltration and a variable degree of fibrosis with architectural distorsion (Fig. 19.8).

Differential Diagnosis

Localized lesions can evoke a common-germ pneumonia or tuberculosis. Paraffinoma, with its radiological characteristics often mimes a malignant tumor.

The diffuse, bilateral forms should lead to investigating all interstitial lung diseases.

Tumors containing fats – hamartomas, lipomas, lipochondromas – must also be eliminated.

Finally, before concluding an exogenous origin, lipoid pneumonia must be examined for any condition that can be responsible for endogenous lipoid pneumonia.

Natural History and Complications

With treatment, acute ELP (fire-eater's pneumonia, single accidental inhalation) can show clinical and radiological improvement.

The course of the other forms of ELP is chronic and often asymptomatic. As is often the case, they are discovered by chance and can then evolve towards chronic respiratory failure and death if the lesions are extensive and go undiagnosed.

Acute respiratory failure cases have been described, either in acute accidental forms or in the course of chronic forms.

They highlight various complications:

- Superinfections are rarely proved and may be diagnosed in excess due to clinical presentation with low-grade fever, cough and sputum. However, superinfections by nontuberculous mycobacteria must be mentioned. First described in 1967 [12], several cases have been reported since then [34]. This condition is probably facilitated by lipids, which enhance the growth of these organisms.
- Hemoptysis varies in amount, with a few cases of massive hemoptysis [35], and are either spontaneous or subsequent to bronchial biopsy in contact with the lesion.
- Association with bronchial cancer, in which some authors incriminate the possible carcinogenic role of the oils, or "scar cancer", while others consider this association fortuitous [36, 37].
- Hypercalcemia, which can be explained by the production of calcitriol from inflammatory cells, as in other granulomatous diseases such as sarcoïdosis or tuberculosis [38].
- ELP in children may be complicated by bronchectasis [39].
- Finally, a case of hypertrophic osteoarthropathy has been described in children with chronic ghee oil intoxication [40].

Treatment

The basis of treatment is to recognize the oily substance responsible and to discontinue exposure to it. This will allow to stabilize or improve the lesions or even make them disappear. But most often, the imaging abnormalities last and remain

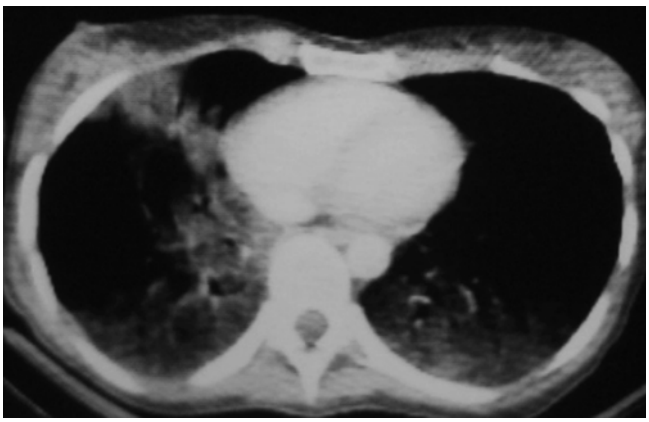

Fig. 19.9 CT scan (mediastinal window). Bilateral alveolar condensations with hypodense aspect

unchanged for years even if the causative exposure has been terminated, contrasting with the usual outcome of conditions due to exogenous exposure (such as hypersensitivity pneumonitis or drug-induced lung diseases). Despite the elimination of intoxication, ELP may also deteriorate if the lesions are extensive at the time of diagnosis.

Predisposing factors such a gastro-oesophageal or abnormalities of upper aerodigestive tracts must also be treated.

Other medical measures should be considered:

- Daily respiratory physiotherapy to eliminate the oily substance [41].
- Oral corticosteroid therapy to slow down inflammatory reaction, although this treatment has shown mixed results and remains controversial.
- Therapeutic BAL, as used in symptomatic alveolar proteinosis, has been used successfully in extensive ELP [42, 43].
- When bronchiectasis in children is caused by lipoid pneumonia and does not respond to medical treatment, surgical resection is recommended [44].

Preventive treatment is also essential:

- Patients must be informed of the danger of using large quantities of oily medicines over long periods. This message is often ignored because self-medication is frequent in the diseases concerned (constipation, chronic rhinitis…)
- Prevention is important in the workplace, especially when paraffin or other oily substances may be sprayed.

Conclusion

ELP are uncommon, often asymptomatic, diseases. The most frequent etiology is the chronic use of medicines containing mineral oily substances, mostly paraffin or vaseline, for constipation or rhinopharyngeal diseases.

Diagnosis of ELP must be considered when patient history and imaging features suggest it and confirmed by various examinations allowing to show presence of intrapulmonary oil. Endogenous lipid pneumonia must also be eliminated.

Early recognition and discontinuation of exposure are essential to prevent the lesions from evolving towards fibrosis and respiratory failure.

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Pulmonary Alveolar Microlithiasis

20

Salvatore Mariotta, Alessandro Onofri, Pierdonato Bruno, and Alberto Ricci

Pulmonary alveolar microlithiasis (PAM) is a rare disease characterized by the progressive accumulation of calcific elements, the microliths or calcospherites, into the alveolar spaces.

History of PAM

The histopathological features of this disease were described for the first time in 1918 [1]. while the Roentgen findings were reported in 1932 [2]. In 1933, this condition was defined "mikrolithiasis alveolaris pulmonum" [3] but a complete description of the disease was given only in 1947 [4]. In the following 50 years, many other papers have been published about the clinical, radiological and metabolic features of PAM and about the diagnostic procedures used to identify the disease. In 1957, the international literature on this subject was reviewed for the first time and was published a paper analyzing 44 cases of PAM [5]; a similar paper concerning 120 cases was published in 1968 [6]. Turkish (52 cases) and Italian (48 cases) case reports were reviewed respectively in 1993 [7] and in 1997 [8]. In 2002 [9] and 2004 [10] the case-reports published in the literature were studied highlighting most important aspects of the disease such as the incidence in various countries, age, symptoms, detection and treatment used hitherto. Family history for the disease was found in one third of the cases (up to 6 cases in the same family [11]); today the disease is considered as an inherited autosomal recessive illness [9]. In 2006 the mutation of the gene *SLC34A2*, involved in the metabolism of surfactant phospholipids, was considered responsible of the onset of the disease for the first time [12]. Studies confirming this hypothesis are appearing in the literature [13, 14]. An effective therapy of this pathologic condition is not yet available.

Epidemiology

There haven't been any epidemiological studies of the disease and our current knowledge regarding the prevalence comes from the case reports published in the literature. The disease has long been considered characteristic of people of the Mediterranean area and, in particular, it was thought of as a Turkish and/or Italian illness, however the international literature suggests PAM is an ubiquitous disease [9, 10]. The updating of the case reports published up to 2003 [9] together with the data reported in literature between 2004 and 2012 shows a total of 670 cases distributed in all continents, with a marked prevalence in Europe (41.5 %) and Asia (38.8 %). Few PAM cases result from America (12.9 %), Africa (3.7 %) and Australia (0.9 %) (Fig. 20.1). Fifty-six countries were affected and 13 were assigned a number of cases greater than 10: Brazil (14), Bulgaria (19), France (32), Germany (36), India

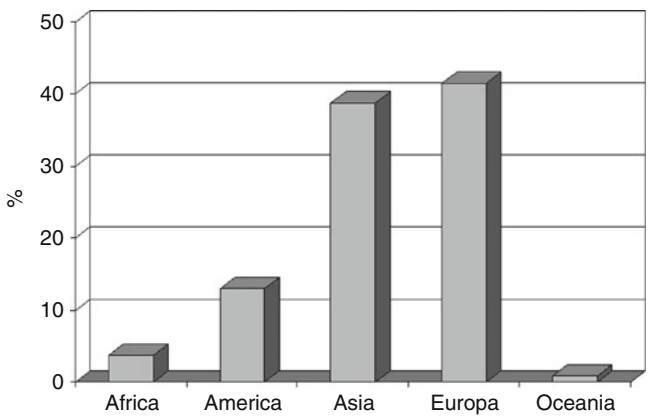

Fig. 20.1 Cases of pulmonary alveolar microlithiasis in the international literature: subdivision by continent (656 pts. out of 670)

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(50), Italy (64), Japan (42), Poland (11), Russia (37), Spain (36), Turkey (105), USA (47), Ex Yugoslavia (11) (Table 20.1).

Reviews on Turkish and Italian cases [7, 8] show that almost half of the cases were only published in local journals and that the true incidence of PAM has probably been underestimated. The majority of cases involved students, since the disease develops mainly in the first decades of life (Fig. 20.2); however housewives, office employees, workers etc. were also involved. PAM was described in association with other diseases, e.g. mitral stenosis, kidney stones or calcifications in the seminal vesicles or other organs [9]. Furthermore, the disease does not seem to only affect humans and it also appears to occur in some animals such as orang-tangs, dogs, sheep, cats, nakt mice, Afghan pika.

Etiopathogenesis

Many observations support the hypothesis that a familiar inherited trait is involved according to an autosomal recessive transmission. Several cases (up to six) were diagnosed in the same family [11]. Family occurrence was found up to 31.4 % and most cases were siblings. Other authors [5, 7] found this percentage to be higher. The difference could be due to the absence of family screening for educational or economic reasons, especially in the developing countries.

In the past it was assumed that calcium salt deposits in the alveoli were due to changes in calcium metabolism because of some unknown defect. The widely endorsed hypothesis suggested an abnormality involving the carbonic

Table 20.1 Cases of pulmonary alveolar microlithiasis from 56 countries

Algeria (5)	India (50)	Peru (9)
Argentina(2)	Iran (6)	Poland (11)
Australia (2)	Iraq (7)	Portugal (1)
Austria (5)	Israel (4)	Russia (37)
Belgium (8)	Italy (64)	South Africa (4)
Brazil (14)	Jamaica (3)	S Arabia (8)
Bulgaria (19)	Japan (42)	Spain (36)
Canada (2)	Kwait (1)	Sri-Lanka (2)
China (8)	Lebanon (5)	Switzerland (4)
Cyprus (1)	Libia (4)	Syria (1)
Columbia (4)	Malaysia (1)	Tanzania (1)
Egypt (2)	Mexico (5)	Thailand (3)
France (32)	Morocco (6)	Tunisia (1)
Germany (36)	Nigeria (2)	Turkey (105)
Great Britain (8)	N Zealand (4)	USA (47)
Greece (5)	Norway (9)	Yemen (1)
Hungary (5)	Pakistan (3)	Ex Yugoslavia(11)
Corea (1)	Giordania (1)	Uruguay (1)
Sweden (1)		

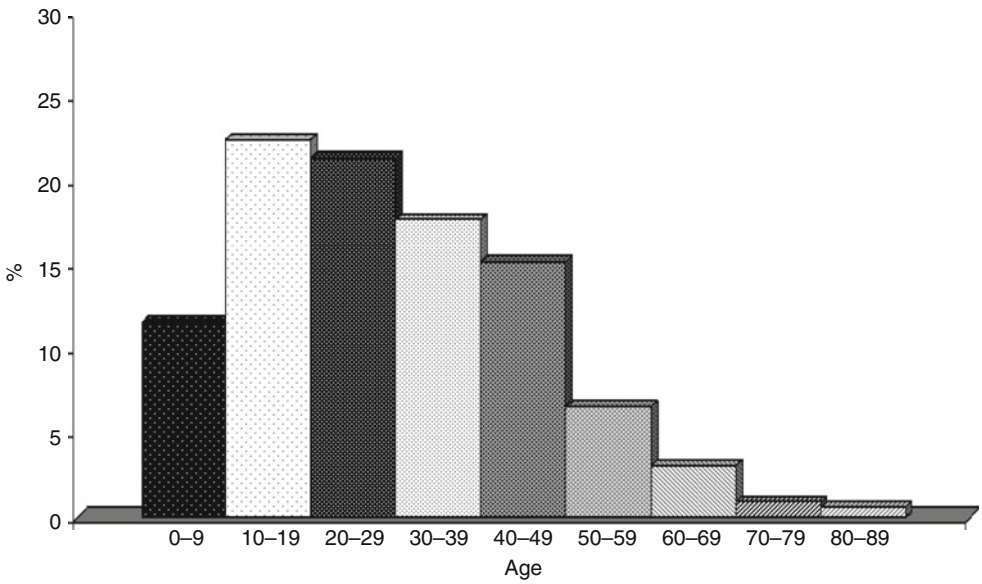

Fig. 20.2 Distribution by age of 643 pts. out of 670 cases of Pulmonary Alveolar Microlithiasis

anhydrase enzyme at the alveolar surface, with consequent alkalinity in the alveoli, calcium precipitation and development of calcospherites. Other hypotheses considered the first step of the disease to be the consequence of the arrival of calcified mycetes, transported into the alveoli by inhaled air; others took it to be the consequence of a diet rich in calcium salts, e.g. milk (milk alkali syndrome), or of the prolonged inhalation of dust or powdered substances ("snuff syndrome"), or changes in pulmonary haemodynamics due to mitral stenosis. Calcium metabolism was reported to be normal in most cases.

In 2006, a mutation of SLC34A2 gene was for the first time proved to occur in PAM patients [12]. This gene is a member of the solute carrier family 34 (sodium phosphate), member 2 – SLC34A2, which plays a major role in the homeostasis of inorganic phosphate [12], and it was shown by immunohistochemistry to be expressed in lungs only in alveolar type II cells, which are responsible for surfactant production [15].

The gene regulates the normal production of type IIb sodium-dependent (NaPi-IIb) phosphate transporter [16]. The function of this protein, encoded by the member 2 of SLC34A gene (SLC34A2), is to uptake liberated phosphate from the alveolar fluid for surfactant production [12]. The type II cells produce pulmonary surfactant, of which phospholipids are essential constituents; outdated surfactant is taken up by type II cells for recycling and degradation, and by alveolar macrophages only for degradation. Degraded phospholipids release phosphate that should be cleared from the alveolar space [17] (Fig. 20.3a). Dysfunction of *SLC34A2* reduces the clearance of phosphate and leads to the formation of microliths composed of calcium and phosphate [13, 18] (Fig. 20.3b).

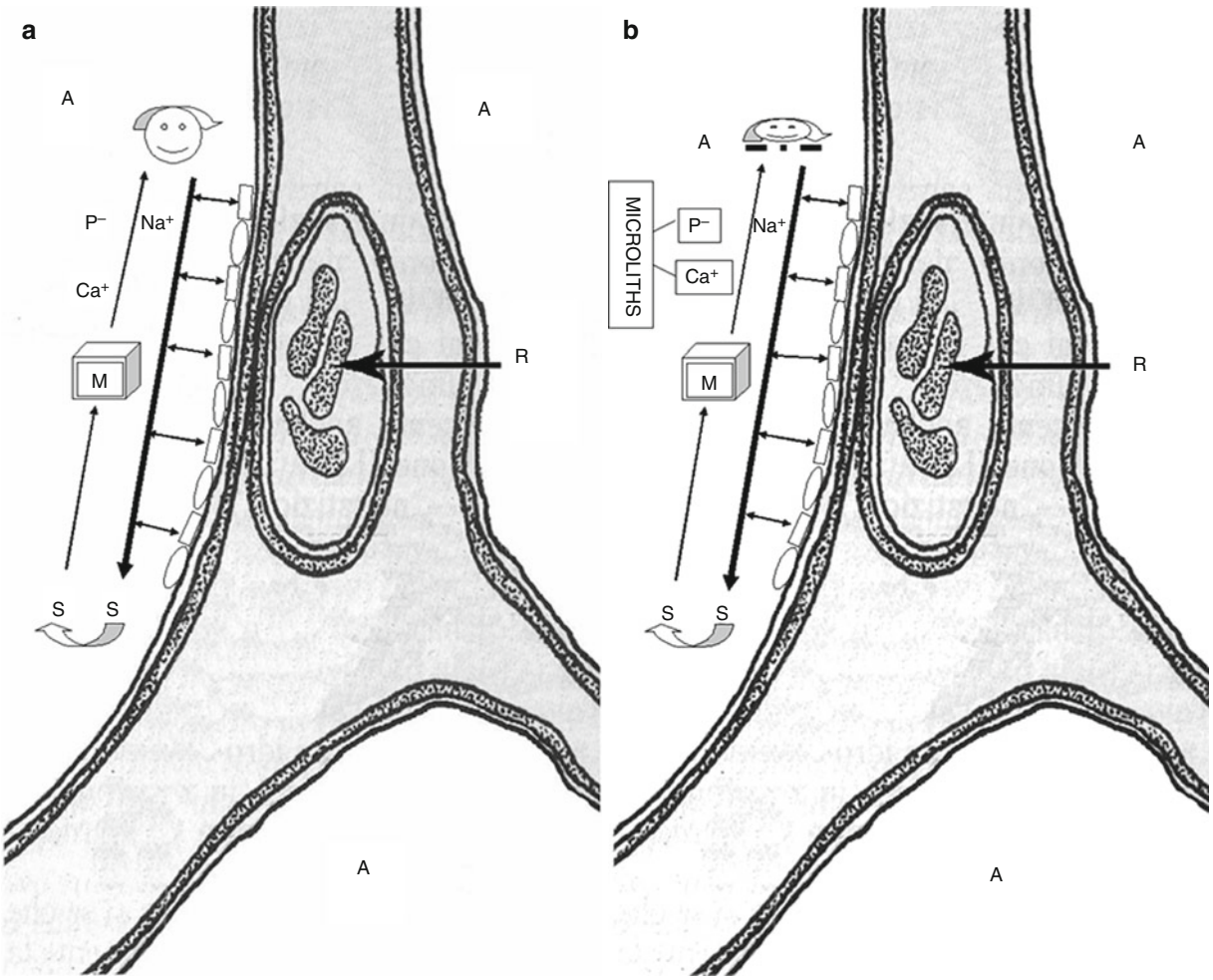

Fig. 20.3 (**a**) Schematic representation of the normal function of the cotransporter protein, coded by *SLC34A2* gene, in the clearance of the surfactant from the alveoli. The type II pneumocytes produce the surfactant and pour it into the alveolar space. Phospholipids are essential constituents of the pulmonary surfactant and the type II cells degrade them and recycle the products of their metabolism. Na^+ and P^- are cleared from the alveolar space by the protein coded by *SLC34A2* gene which co-transports them into the cells. (**b**) Schematic representation of dysfunction of the cotransporter caused by mutation of the gene *SLC34A2*. Dysfunction of *SLC34A2* reduces the clearance of phosphate and leads to the formation of microliths composed of calcium and phosphate. *A* alveolar space; *R* red blood cell

PAM is a recessively inherited disease and is not caused by environmental factors. It has full penetrance, since none of the unaffected members is homozygous for the disease haplotype [12]. The homozygous mutations in *SLC34A2* determine symptomatic PAM, while the heterozygous carriers are asymptomatic. The identification of the gene responsible for PAM facilitates genetic diagnosis and gives hope for a genetic therapy [14, 19].

Pathology

Calcium deposits within the alveoli begin at the lower lobes and in 20–30 years or more they extend to the whole lungs. Calculi have a round or ovoidal shape and range from 0.01 to 2.8 mm in diameter (Fig. 20.4). In the early stages, the alveolar septa are intact and gas exchanges are normal. Microliths progressively increase in number inside the alveoli, until they occupy the entire alveolar space and come into contact with the walls which in the advanced stages are pressed, injured and replaced by fibrous tissue. Upon opening of the chest, lungs reveal an increase in volume and weight, they are not collapsible and, upon cutting, they reveal a granular and irregular surface; the resistance of the lung parenchyma is markedly increased, almost as if it were a stone. This was precisely the picture that Malpighi [19] described in 1686 in the postmortem report of a young man – "…*Pulmones turgidi graves et compactae substantiae inaequaliter nigri. Interius in vesciculis pulmonum innumeri lapilli reperti sunt* …" (The lungs were heavy and compact with patches of black. Countless small stones were found in the interior of the lungs); this has also been identified as the first case of PAM reported in the literature. In all autoptic observations, the weight of the lungs is reported to be significantly increased up to 6.190 kg. Several authors have studied the structure and the composition of the microliths in an attempt to explain the pathogenesis of the disease. So it was thus observed that these concretions are irregularly concentric and laminated, and that they consist of calcium salts. Transmission or scanning electron microscopy of microlith fragments revealed spectra where calcium and phosphorus have peak intensities, and a 2:1 ratio of calcium over phosphorus, which is consistent with a Ca_2PO_3 content. Deposits of iron, zinc, aluminium and magnesium are frequently found in the fragments.

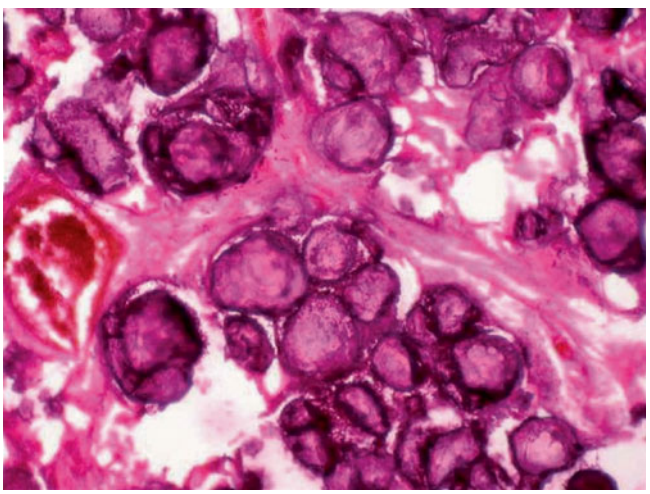

Fig. 20.4 Histopathology section showing multiple calcospherites within the alveoli of lung parenchyma. H and E 100× (Courtesy of Gayathri Devi and coll [20])

Clinical Features and Course

Symptoms and Signs

The age of PAM diagnosis has been reported to vary but it is usually diagnosed under the age of 30 years and the disease develops silently for many years. There are no symptoms in the majority of patients (up to 52.8 % of cases) and diagnosis is often fortuitous. For instance, the diagnosis has often been made during occasional chest x-rays and general check-ups required by employers, or after performing chest x-rays because of late physical or endocrine development in children [9]. Lung function tests are normal for a long time and only in the advanced stage of the disease is there an impairment, due to a restrictive syndrome or a respiratory/heart failure. Symptoms are due to an increasing number of tiny calculi within the alveoli throughout the lungs. Dyspnoea is the most frequent symptom, followed by cough, chest pain and asthenia (Fig. 20.5). It is hypothesized that coughing could be related to the direct stimulation of the C fibers or receptors by the microliths.

Physical examination reveals bilateral crackles and rhonchi. Their extension depends on the stage of the disease: they

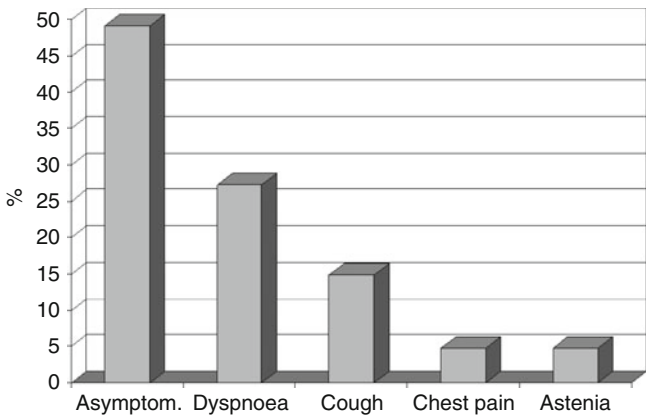

Fig. 20.5 Symptoms at diagnosis in 640 pts. out of 670 suffering from pulmonary alveolar microlithiasis

are limited to the bases in the early stages and extended to the intermediate or high parts of pulmonary fields in advanced stages. Sometimes cyanosis or finger clubbing are the first sign of the disease and in advanced stages cardiac-respiratory failure can worsen clinical features.

Disease Course

As mentioned above, patients may be asymptomatic for many years before appearing the respiratory failure [10]. In some cases, the disease remains apparently static; in others, over time it progresses to pulmonary fibrosis and respiratory failure accompanied by dyspnea and worsening of pulmonary function test [9]. In our experience, the radiological changes (HRCT) and functional ones (spirometry, arterial blood gas analysis) associated with the assessment of symptoms and signs were the only investigations that could assess the risk of disease progression. This is even more important when in the family there are cases of full-blown microlithiasis.

PAM normally progresses within 10–20 years, and most cases have been followed for up to 10 years after initial diagnosis; however, in few cases have been reported follow-up for periods more than 40 years. Chronic inflammation associated with the smoking habit may favour the onset of symptoms while the exacerbations accelerate the development of the disease as occurred in our experience. Thus, smokers have more severe clinical phenotypes than non-smokers [21]. Death typically occurs 10–15 years after diagnosis (mean age within the fifth decade of life). The long-term prognosis is poor in patients with PAM, even in those diagnosed during the asymptomatic phase in childhood. Lung transplantation has been beneficial in patients developing severe respiratory failure and right heart failure, but there are no data or are very poor, about survival after lung transplant [22].

Clinical Vignette

S.F.M., male, 46 years old, insurance broker, no smoker. Six months ago, his sister was diagnosed affected with PAM with a chest x-ray, performed by chance. So, he decided to have a chest x-ray which showed diffuse bilateral micronodular opacities. After 5 years without any symptom this patient started to have dry cough, exertional dyspnoea and peripheral cyanosis and he called for a specialist visit. Physical examination revealed bilateral crackles and rhonchi; chest X-Ray showed the characteristic "sandstorm" picture (Fig. 20.6); blood examination pointed out polycythaemia. Arterial blood gas analysis was characterized by marked hypoxemia. Lung function tests showed a restrictive ventilatory defect: VC = 50 % of predicted, FEV_1 = 52 % of predicted, RV = 94 % of predicted. HRTC scans was obtained revealing the deposition of microliths in all chest fields: in the upper areas, the calcospherites were present in the centrilobular regions while in the lower areas the microliths arrangement was in the peripheral lobular structures showing a typical mosaic picture for fibrotic damage (Fig. 20.7 a–c). Bodyscintscan with 99Tc reveals a diffuse uptake in the lungs. The patient underwent fiberoptic bronchoscopy with bronchoalveolar lavage: BALF analysis revealed an increase in total cell count with a higher percentage of neutrophils, a reduced percentage of macrophages, a normal count of lymphocytes. The mineralogical analysis of BALF showed numerous mineral concretions with 1.77 mm of diameter made of silicates (14 %) and metals (86 %). Patient underwent repeated bronchoalveolar lavage, and he was administered cortisone, cardiokinetic and diuretic drugs, bleeding, oxygen therapy but the treatment was uneffective and symptoms worsen. Sodium etidronate (300 mg t.i.d.) was administered. Despite an initial improvement of symptoms, after 1 year chest x-rays and HRCT features remained unchanged. Patient underwent lung transplantation but he died a few days after for complications from surgery.

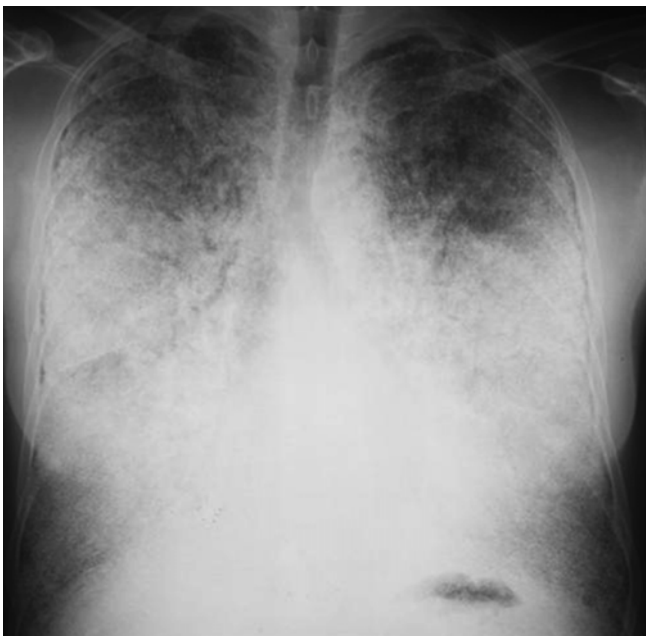

Fig. 20.6 Chest X ray of a 50 year old man suffering from PAM

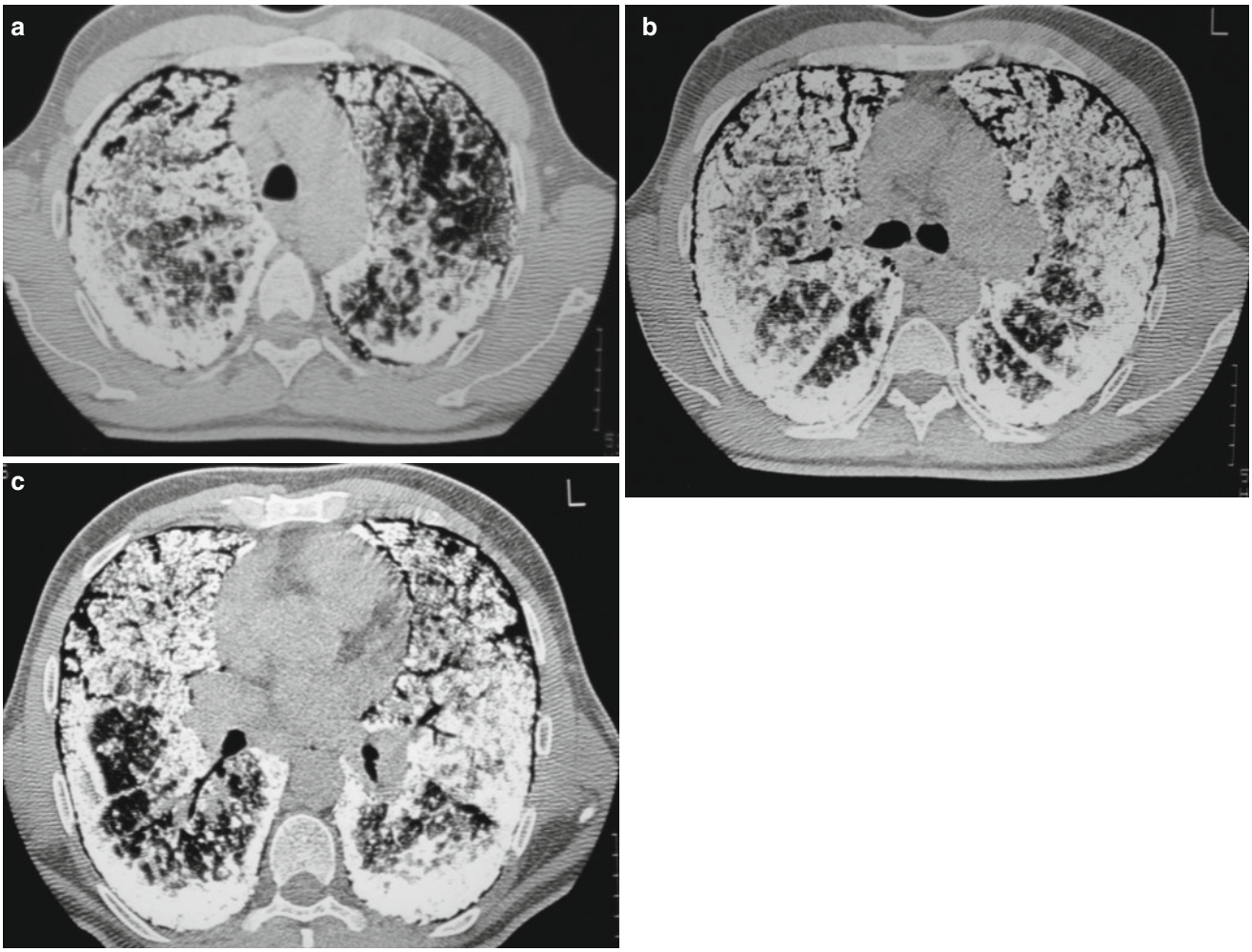

Fig. 20.7 (**a**–**c**) HRCT of a patient with PAM: scans performed at different levels show a widespread involvement of the lung parenchyma

Diagnosis

Microliths can be found in spontaneous or induced sputum, in bronchial wash, or in the fluid of bronchoalveolar lavage. The accumulation of innumerable calculi in the alveoli causes a characteristic radiologic feature, which at first, involves the lower lobes and then the middle and upper areas of the lungs, producing a "sandstorm-like" picture [23]. In advanced stages, the intense radio-opaqueness of the calcium salt deposits shows a "white" lung, with the disappearance of the boundaries between heart and lungs. At the periphery, on the contrary, the lungs are separated from the ribs by a thin dark line because of the presence of subpleural air cysts, which sometimes cause the pneumothorax. HRCT (High Resolution Computed Tomography) confirms the radiographic findings, showing the thickening of interlobular septa, bronchovascular bundles, and pleura. Particularly, at least in advanced stage, microliths are distributed within the perilobular interstitium. Subpleural multiple small cysts are also common [24]. Chest x-rays and CT scans are so characteristic (Figs. 20.1 and 20.2 a-c) that several authors think these tests are sufficient for diagnosis especially when there is a case of PAM in the family. Body scintscan with 99Tc reveals a diffuse uptake in the lungs (Fig. 20.8) due to hydroxyapatite crystals. In the past, the disease was often misdiagnosed as tuberculosis, with patients often undergoing long-term antitubercular treatment. Histologically, PAM can be diagnosed by means of a lung biopsy through thoracotomy, through the transbronchial or transparietal route, and through necropsy (Table 20.2). PET-TC did not shows high pulmonary uptake of radionuclides in both lungs sparing calcifications [25].

In conclusion PAM is usually suspected on the basis of a typical picture of chest radiograph and HRCT, namely a very

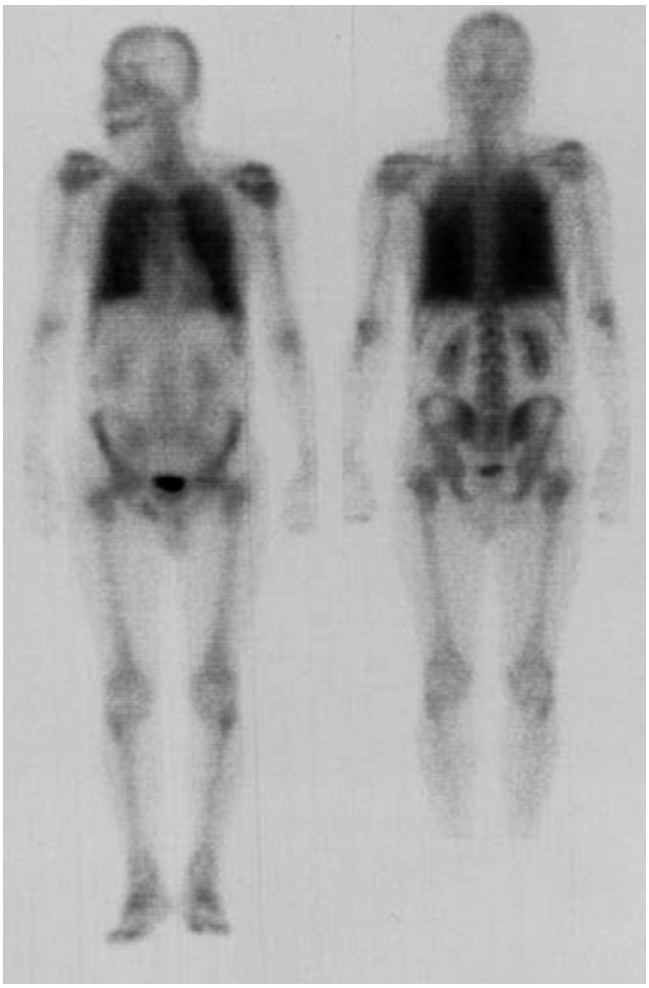

Fig. 20.8 Bone scintiscan with technetium99 of PAM showing diffuse uptake in both lungs

fine micro-nodulation of calcific density diffusely involving both lungs, with basal predominance. Many authors argue that this radiological pattern, sandstorm like, precludes the need for a lung biopsy in most cases [21]. Then, the diagnosis can be confirmed by demonstrating the presence of microliths in the sediment of the bronchoalveolar lavage (BAL) or in transbronchial biopsy.

The molecular diagnosis is not necessary for the definitive diagnosis and, in literature, comparisons between radiological and molecular results are not reported. Furthermore, this investigation is not easy to perform and there are currently few centers able to perform it. (Genetic diagnosis and cell therapy center Acibadem healthcare group, F KerimGokay Cad. No49 – Altunizade Uskudar 34662, Istanbul Turkey; ORPHA 100700; Unidad de Genotipado y Diagnostico Genetico, Hospital Clinico Universitario de Valencia – Av Blasco Ibanez 17 46010 Valencia Spain, e-mail: a.barbara.garcia@uv.es, ORPHA 278839).

Differential Diagnosis

Although the typical radiological pattern could lead to diagnosis of PAM, other pathologic conditions with diffuse pulmonary involvement should be considered for differential diagnosis as pulmonary alveolar proteinosis, amyloidosis, diffuse pulmonary ossification.

In pulmonary alveolar proteinosis, CT scan shows consolidation of the air spaces, with thickening of the interlobular septa, producing the so-called "crazy paving" appearance [26]. Analysis of the BALF sediment shows a few inflammatory cells and PAS positive reaction, presence of large acellular eosinophilic bodies on a diffuse background of basophilic granular material.

In pulmonary amyloidosis, single or multiple nodules, localized in the lower lobes, are found; calcifications are

Table 20.2 Practical empiric criteria used for the diagnosis of pulmonary alveolar microlithiasis

Diagnostic criteria
Major criteria:
Signs and symptoms: Bilateral crackles, cyanosis and finger clubbing. Dyspnoea, dry cough, chest pain, asthenia, mean age <40 years
Chest radiography: "Sandstorm" appearance which involves the lower lobes and then the middle and upper areas of the lungs
High-resolution computed tomography: Diffuse ground- glass attenuation and subpleural linear calcifications, microliths are distributed within the perilobular interstitium
BAL: Shows the characteristic calcospherites in the recovered fluid (BALF)
Decreased DLCO and restrictive syndrome
Histology: Shows microliths in lung biopsy
Minor criteria:
Bone scintigraphy with technetium (Tc)-99m methylene diphosphonate
Magnetic resonance imaging: Hypointensity or a signal void on T1- and T2- weighted images
18F-FDG-PET/CT

seen in 20–50 % of cases and they are often centrally or in an irregular pattern within the nodule [27, 28]. Lung biopsy is necessary for the diagnosis along with the presence of immunoglobulin-free light chains in serum.

Furthermore, PAM must be distinguished by a rare condition called diffuse pulmonary ossification a form of metaplastic mature bone formation in the lung parenchyma [29]. This is a rare clinical condition, usually asymptomatic. It occurs around the fourth to sixth decade of life in the setting of other lung diseases; rarely, it is a primary idiopathic form. The diagnosis is often made only at autopsy, being misdiagnosed in life. Clinical data are limited only to fatigue, a restrictive functional impairment with reduced transfer factor (DLCO). It is difficult to highlight this condition on chest radiograph and CT scans but is necessary to use the high resolution CT (HRCT) for the decisive diagnosis. Two types of widely disseminated or ossification are described: "dendriform", can be detected on HRCT as multiple tiny branching calcifications that do not conform to a recognisable anatomical or lobular configuration, and "nodular" which tends to be more circumscribed and situated in alveolar spaces. The HRCT feature of disseminated dendriform pulmonary ossification was found on HRCT in 5 out of 75 patients with usual interstitial pneumonia (UIP) and in none of 44 patients with non specific interstitial pneumonia (NSIP); this corresponded histopathologically to multiple dendriform nodules of mature bone embedded in fibrous stroma in basal, subpleural areas of fibrosis and honeycombing [30]. The main radiological difference between PAM and disseminated dendriform pulmonary ossification is that in the second condition we have the characteristic branching nature of the heterotopic bone formation within areas of fibrosis while in PAM we have the sand-like micronodulation bilaterally and the typical pleural or subpleural cysts and calcifications.

Therapeutic Attempts

Even today, most therapies have proved ineffective. Some authors have tried to remove the microliths by repeated bronchoalveolar lavages. However, the amount of microliths removed with BAL is very poor and only induces minor changes on chest x-rays or CT scans. Bronchoalveolar lavage probably only removes microliths having smaller diameters than the calibre of the alveolar ducta, while it is ineffective against microliths inside the alveoli that are one size larger. Other authors have tried to break down the microliths with sodium etidronate. However the results were not very encouraging, since the chest x-rays were stationary after therapy and there were no clinical advantages. It was only recently that a little girl, suffering from PAM and taking sodium etidronate at the dose of 10 mg/kg for 10 year, showed a reduction in the calcified opacities in the lower lobes [31]. At the moment, the only effective therapy is lung transplantation, especially when the replacement is made before the advanced stages of the disease [32, 33].

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Pulmonary Fibrosis and the Many Faces of UIP

21

Stefania Cerri, Giacomo Sgalla, Giulio Rossi, Giovanni Della Casa, and Luca Richeldi

Introduction

Interstitial lung diseases (ILDs) represent a heterogeneous group of clinical entities among which disease of unknown causes may mimic ILDs due to known causes [1]. Clinical, radiographic and histopathology presentation can largely overlap between different entities and a multidisciplinary approach is proven to be essential in composing the puzzle to reach the most likely clinical diagnosis in each single patients [2]. The definition of specific radiographic (on chest high-resolution computed tomography, HRCT) and histopathology (on lung surgical lung biopsy, SLB) patterns has provided a common terminology in the field of ILDs in the tentative of classifying entities presenting with distinctive features. These patterns have been proposed in the classification of idiopathic interstitial pneumonias (IIPs) [3], and then have been applied to describe ILDs due to secondary known causes, particularly those related to connective-tissue diseases. Among all these patterns, the usual interstitial pneumonia (UIP) pattern has received more emphasis, in particular since it identifies patients with idiopathic pulmonary fibrosis (IPF), as outlined in the most recent evidence-based international guideline [4]. In this document, specific HRCT and SLB criteria for the definition of a definite UIP pattern have been proposed and since then they have been widely used as reference standard both in clinical practice and in the definition of eligibility criteria for randomized clinical trials. However, while a definite UIP pattern can be diagnostic for IPF in the proper clinical context, it is well known that the same pattern can be present in fibrotic lung diseases other than IPF, with important consequences in terms of therapeutic management and prognosis. This chapter will provide an overview on how the UIP pattern is defined, both on radiologist's view and on pathologist's view, along with elements that might be helpful in distinguishing an idiopathic UIP pattern from similar appearance in secondary diseases.

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The Radiologist's View: UIP Pattern on HRCT Scan

Chest HRCT represents today the essential component of the diagnostic process in idiopathic ILDs. In the appropriate clinical settings, the identification of a definite UIP pattern on chest HRCT is considered to be diagnostic for IPF and therefore does not require further confirmation [4, 5]. In this context, it is extremely important that HRCT acquisition fulfills the technical requirements that allow for the best interpretation of parenchymal abnormalities. In the international evidence-based IPF guidelines published in 2011 [4], the committee members (including expert radiologists) provided a summary of the technical specifications that should be used in an optimal HRCT exam aimed at identifying the changes characteristics of the UIP pattern. The technical specifications are listed in Table 21.1.

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Table 21.1 HRCT technical requirements for evaluating radiologic patterns in interstitial lung diseases

HRCT technical requirements
Scans without contrast
Full inspiration without respiratory motion
Contiguous or noncontiguous axial scans with thin sections, reconstructed at ≤2 cm intervals
Reconstructed slice collimation ≤2 mm
High resolution reconstruction algorithm
Field of view to include lungs only
Expiratory scans, to exclude lobular air trapping suggestive of hypersensitivity pneumonitis
Prone scans if dependent density obscures detail on supine images
Optional coronal and sagittal reconstructions if volumetric images are obtained

Modified from Ref. [4]

According to these guidelines, a definite UIP pattern on chest HRCT can be identified when all the following features are present: (1) subpleural, basal predominance; (2) reticular abnormalities; (3) honeycombing with or without traction bronchiectasis and (4) absence of features that are inconsistent with a UIP pattern (such as any of the following: upper or mid-lung predominance, peribronchovascular predominance, extensive ground glass abnormality, profuse micronodules, discrete cysts away from areas of honeycombing, diffuse mosaic attenuation/air trapping, segmental or lobar consolidation) [4]. The presence of features one, two and four in the absence of honeycomb changes defines a possible UIP pattern, which should require confirmation with SLB in order to achieve a final diagnosis.

Therefore, a HRCT UIP pattern should be considered in patients who present with low lung volumes, subpleural reticular opacities, honeycombing with or without traction bronchiectasis, the extent of which increases from the apex to the bases of the lungs. In a patient with a definite UIP pattern on chest HRCT, the disease is most extensive on lower sections. Typically, imaging findings of a UIP pattern are heterogeneous, with areas of more or less dense fibrosis alternating with areas of normal parenchyma. The dominant finding is represented by honeycombing, a critical element for the definition of definite UIP on HRCT. According to the definition of the Fleischner Society, honeycombing consists of clustered cystic air spaces typically of comparable diameters in the order of 3–10 mm, but occasionally as large as 2.5 cm. It usually has a subpleural distribution with well-defined shared walls [6]. The finding of honeycombing generally implies the presence of established (and therefore irreversible) lung fibrosis.

Although the presence of honeycombing makes an important difference in identifying a definite UIP pattern according to current guidelines, more recent data might question the ability of even expert radiologists of agreeing in the identification of such a finding on HRCT [7]. The presence of traction bronchiectasis (which are also a critical component in the radiological definition of the UIP pattern) or superimposed emphysema represents major causes of disagreement, with resulting low diagnostic agreement. Multiplanar image reconstruction might be helpful in distinguishing definite honeycombing from its mimics, particularly from traction bronchiectasis or bronchiolectasis in the context of surrounding extensive pulmonary fibrosis. As per authors' admission, the differentiation between true honeycombing and traction bronchiectasis might be subjective, and the presence of a combination of both is also a possibility, making the distinction virtually impossible [7]. However, whether different imaging criteria for the definition of honeycombing have any impact on patients' prognosis is presently unknown and requires further investigation, particularly in the context of more recent data suggesting that traction bronchiectasis are critical elements in predicting clinical course in ILDs.

On the other hand, we know that the positive predictive value of a HRCT diagnosis of UIP is as good as up to 90–100 % [8–13] when compared with SLB pathology, therefore a UIP pattern on HRCT is highly accurate for the presence of UIP pattern on surgical lung biopsy. If honeycombing is absent, but the imaging features otherwise meet criteria for UIP, the imaging features are regarded as representing possible UIP, and, if clinically indicated, SLB is recommended to increase diagnostic accuracy. A recent assessment of HRCT images from patients screened for the inclusion in an IPF randomized control trial has demonstrated that, in the proper clinical setting and in the context of a high radiological expertise in ILDs, even a possible UIP pattern on HRCT can be predictive of a definite UIP pattern on histology. These data would suggest that, upon careful assessment of each individual case by expert clinicians and radiologists, surgical lung biopsy might be avoided in some cases, in which HRCT demonstrates a possible UIP pattern [14]. Further confirmation of these data in other cohorts would be crucially important. Moreover, it is relevant to remember that even in patients whose chest HRCT doesn't fit with a UIP pattern, a SLB may still show UIP pattern on histopathology.

Ground-glass opacities can be present in many patients with a UIP pattern but in the context of IPF usually they are less prevalent than honeycombing and reticular abnormalities [15–17]. If ground-glass opacities predominate, an extensive search for a diagnosis other than IPF should be undertaken. Similarly, the presence of micronodules, air trapping, non-honeycomb cysts, consolidation, or a peribronchovascular-predominant distribution should lead to consideration of an alternative diagnosis [18, 19]. Chest radiograph is less useful than HRCT in evaluating patients with suspected IPF [8], and in fact it can be completely normal in patients with early disease. In advanced disease, the chest radiograph shows non specific decreased lung volumes and subpleural reticular opacities that increase from the apex to the bases of the lungs [20].

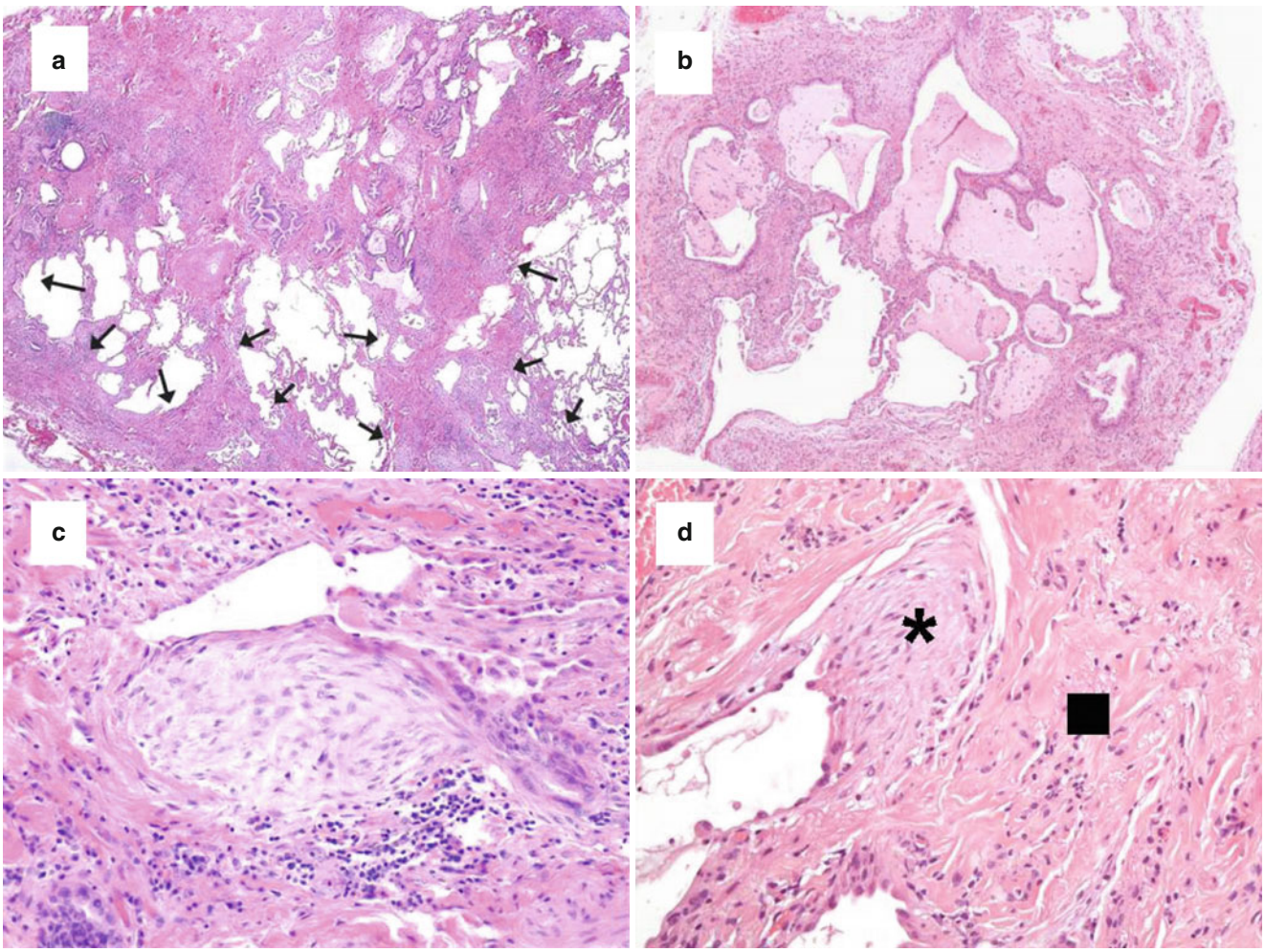


Fig. 21.1 Histologic features of UIP. The patchwork pattern characterized by scarred fibrosis (*arrows*) abruptly alternated by normal lung with main involvement of peripheral subpleural areas and paraseptal regions (**a**, haematoxylin-eosin × 40). Honeycomb changes with enlarged airspaces filled by mucus and inflammatory cells and surrounded by scarred fibrosis and lined by bronchiolar-type epithelium (**b**, haematoxylin-eosin × 100). Fibroblast focus representing the active phase of fibrosis with longitudinally-oriented myofibroblasts in a myxoid matrix covered by hyperplastic pneumocytes or bronchiolar epithelium (**c**, haematoxylin-eosin × 200). Active (*asterisk*) and old fibrosis (*square*) abruptly alternated (**d**, haematoxylin-eosin × 200)

The Pathologist's View: UIP Pattern on Lung Biopsy

The morphologic diagnosis of UIP pattern is no longer the gold standard in IPF, since (as outlined above) in recent years HRCT has provided reproducible information in confirming such a diagnosis in the majority of cases. In other words, accuracy of HRCT in a typical case of IPF is almost perfect and histology is not necessary. However, histology still has a role when HRCT is not typical for a definite UIP pattern, since the differential diagnosis between IPF and NSIP has important prognostic and therapeutic consequences.

On histology, the UIP pattern is a non uniform fibrotic process with subpleural and paraseptal scarred fibrosis irregularly and abruptly juxtaposed to normal lung (spatial heterogeneity with patchwork pattern) (Fig. 21.1a) and this finding is particularly evident at low magnification. Lung architecture is distorted with honeycomb changes (Fig. 21.1b) characterized by enlarged airspaces lined by metaplastic bronchiolar-type epithelium and filled with mucus, neutrophils, macrophages and/or giant cells with intracytoplasmic cholesterol cleft. Seminal papers have highlighted the most important features characterizing a UIP pattern on histology [21–23]. All expert pulmonary pathologists agreed in recognizing three key features: (1) patchy involvement of lung parenchyma consisting of alternating areas of scarred and normal tissues; (2) architectural distortion with/without honeycombing appearance; and (3) the finding of active fibroblastic foci abruptly adjacent to old, dense fibrosis. In advanced/end stage UIP pattern, the lung architecture is completed obscured by diffuse honeycombing and smooth-muscle scars without interposed normal lung. The hallmark of the active fibrotic process is represented by fibroblastic

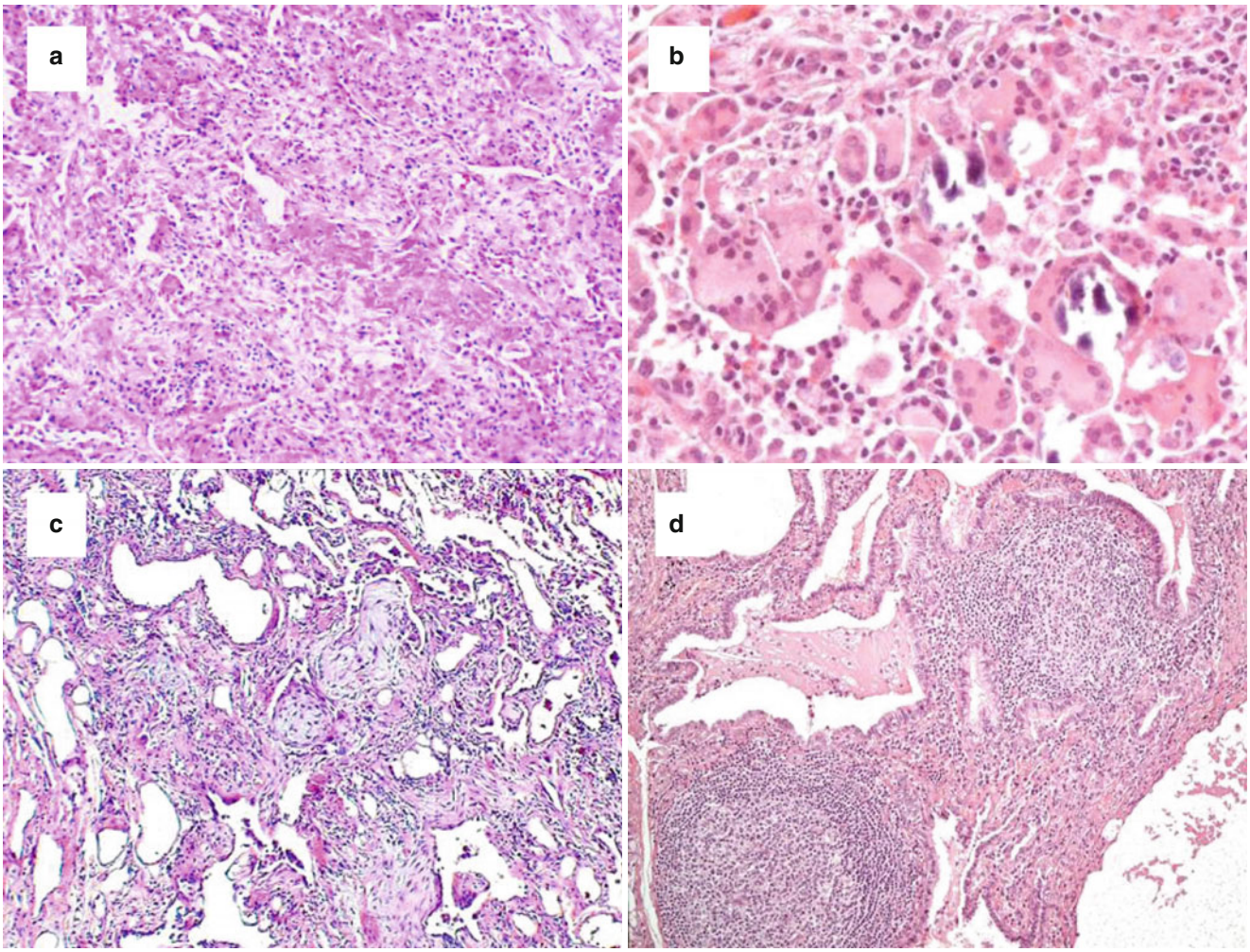


Fig. 21.2 Morphologic features excluding a UIP pattern, such as hyaline membranes (**a**, haematoxylin-eosin × 100), granulomatous inflammation ± giant cells (**b**, haematoxylin-eosin × 200), organizing pneumonia (**c**, haematoxylin-eosin × 100), and marked inflammatory infiltrate (**d**, haematoxylin-eosin × 200)

foci (Fig. 21.1c), consisting of dome-shaped proliferation of myofibroblasts into a myxoid stroma, often covered by hyperplastic pneumocytes or bronchiolar cells. The "young" active fibrosis is easily appreciated as small spots of "gray-to-blue" hematoxylinophilic colour into an "old" remodelling fibrosis with a typical "pink" eosinophilic colour. This peculiar alternation of "old" (fibrotic scars and honeycombing) and "young" (fibroblastic foci) fibrosis leads to the concept of temporal heterogeneity (Fig. 21.1d).

Two concepts that have been stressed by the evidence-based IPF guidelines [4] concern the level of confidence for a diagnosis of UIP and the introduction of exclusion criteria for UIP. Four main histopathologic criteria have been identified: (1) architecture distortion by scarred fibrosis with or without honeycombing; (2) patchwork pattern; (3) fibroblastic foci; (4) lack of features excluding UIP pattern. Based on these features, four categories/levels of confidence have been proposed: (a) definite UIP, which requires the presence of all four criteria; (b) probable UIP, requiring the presence of features one and four, or the presence of honeycomb changes only due to an end-stage fibrotic disease; (c) possible UIP, requiring the presence of features two and four; (d) not UIP, due to the presence of several histologic features (exclusion criteria) which stands against a UIP pattern, such as hyaline membranes (Fig. 21.2a), granulomas (Fig. 21.2b), organizing pneumonia (Fig. 21.2c), a marked inflammatory infiltrate away from honeycombing (Fig. 21.2d), airway-centred changes, other features suggesting an alternative diagnosis (e.g. asbestos bodies) (Table 21.2).

Histologic examination for the evaluation of the presence of a UIP pattern is usually performed on SLB. As such, the pathological criteria for the definition of a UIP pattern, proposed in the 2011 evidence-based IPF guidelines [4], apply only to SLB samples. The ability to select different sites (biopsies should be taken from at least two different lobes) with deep and large biopsies based on a previous accurate HRCT analysis is mandatory to prevent sampling errors and misleading diagnoses [24, 25]. IPF is heterogeneous, often

Table 21.2 Histology of UIP according to the 2011 ATS/ERS/JRS/ALAT IPF Guidelines [4]

Definite UIP	Probable UIP	Possible UIP	Not UIP
1+2+3+4	1+4 or Honeycombing only (end-stage lung)	2+4	5

Abbreviations: *1* architectural fibrotic distortion ± honeycombing, *2* patchwork pattern, *3* fibroblast foci, *4* lack of non-UIP features, *5* presence of hyaline membranes[a]/organizing pneumonia[a, b]/granulomas[b]/marked inflammatory infiltrate away from honeycombing/airway-centered changes/other features favoring an alternative diagnosis
[a]These features may be present in acute exacerbation of IPF
[b]Few/occasional granulomas or minimal organizing pneumonia may be rarely seen in UIP pattern

affecting people with smoking history; therefore the finding of areas showing an NSIP pattern or smoking-related changes along with features of UIP should be taken in account. However, prognosis is basically related to the finding of UIP, even when UIP pattern represents the minor fibrotic component [26–28].

While SLB remains the standard technique for identifying a UIP pattern on histology, some preliminary results indicate a possible role of transbronchial lung biopsy (TBLB) [29]. In a recently published retrospective experience [30], the authors evidenced that histopathologic criteria to suggest a UIP pattern (i.e. at least one feature among patchy interstitial fibrosis, fibroblast foci, honeycomb changes) were present in 30 % of all UIP cases. Sensitivity increased with a higher number of biopsies and the size of specimens, and the agreement between two expert pathologists was good (kappa = 0.61). However, TBLB may be performed only in selected cases and further prospective studies are needed in order to assess the actual sensitivity and specificity of TBLB for the diagnosis of a UIP pattern.

On the other hand, despite a representative tissue sampling, another possible limitation in recognising a UIP pattern on histology is related to the great inter-observer variability among pathologists (mirroring what was described above for chest radiologists). Several studies have highlighted that inter-observer agreement is better, but far from being perfect, among expert pathologists as compared to non-expert pathologists, and very low when comparing experts and non-experts [31–33].

From Patterns to Clinical Diagnosis

The UIP Pattern in IPF

The 2011 evidence-based IPF guidelines [4], and the previously published documents such as the Consensus Statement for Classification of Idiopathic Interstitial Pneumonias (IIP) [3], provide a common framework to interpret radiology and pathology features in terms of patterns and to translate patterns into clinical diagnoses of an idiopathic ILD. In the proper clinical setting, the demonstration of a definite UIP pattern at chest HRCT and/or at SLB is considered diagnostic for IPF, the ILD with the worse prognosis. Therefore, the first request that clinicians address to radiologists and pathologists is to differentiate a UIP pattern from non-UIP pattern, since, in the absence of secondary causes of ILD, the recognition of a UIP pattern leads to the clinical diagnosis of IPF. By combining radiologic patterns with histology patterns, the guidelines on IPF diagnosis and management have proposed a scheme to assign a diagnosis of IPF according to a scale consisting of different degrees of confidence [4]. While it is allowed to attribute a diagnosis of IPF based on a definite UIP pattern on HRCT in the absence of histology confirmation, given the high positive predictive value of HRCT, it has been recognized that, upon multidisciplinary discussion, IPF may be diagnosed also on biopsy-proven UIP in an asymptomatic patient lacking imaging features of UIP, in the effort to recognize and treat patients with early disease.

It is important to state for the pathologists (and clinicians too) that the diagnostic classification according to the levels of confidence in the final diagnosis and the terminology proposed in the 2011 IPF guidelines [4] are important and useful in allocation of cases in clinical trials, while labelling a UIP pattern and therefore a diagnosis of IPF with a level of confidence may not be feasible or even appropriate in the routine practice. In fact, these levels of confidence, mostly derived from retrospective studies, have not been yet validated and basically have a conceptual value in indicating how the pathologist is certain about a UIP pattern rather than being of practical use.

The UIP Pattern in Other ILDs

A UIP pattern on HRCT and/or histology does not always lead to a clinical diagnosis of IPF. In fact, it should be reminded that similar radiologic or pathologic patterns may be seen in idiopathic and non-idiopathic interstitial pneumonias, therefore the simple recognition of any given pattern does not exempt from a careful evaluation for possible secondary causes of ILD. For example, a UIP pattern on HRCT is not exclusively seen in IPF, as it can be the distinctive feature also in the case of lung involvement in connective-tissue disease (CTD), particularly in rheumatoid arthritis-associated interstitial lung disease [34], in chronic hypersensitivity pneumonitis (HP) [35], or in mineral dust-related interstitial lung disease, such as asbestosis [36]. Despite a great extent of overlap in UIP pattern from different clinical entities, some peculiar features might be helpful in suggesting alternative diagnosis, particularly when chronic HP and CTD-ILD can be suspected [37]. For exam-

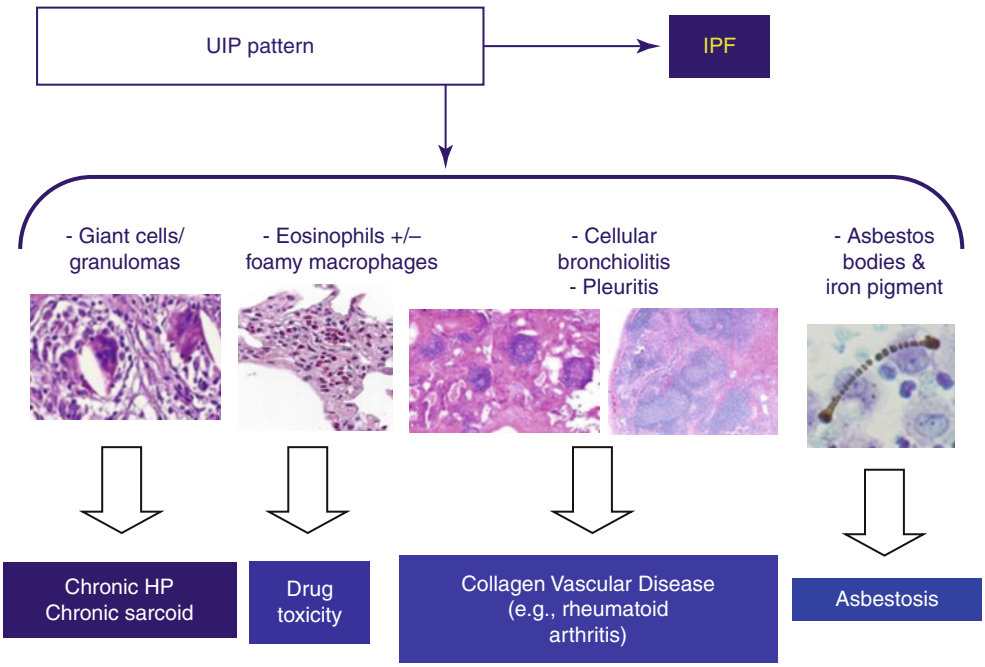


Fig. 21.3 UIP pattern in idiopathic/IPF and non-idiopathic interstitial lung diseases

ple, the presence of lobular areas of decreased attenuation and centrilobular nodules, along with the absence of distinct lower zone predominance of abnormalities, appear to be helpful in differentiating IPF from chronic HP on HRCT in approximately 50 % of patients [38], although the causative antigen might remain unknown in a sizeable proportion of patients with histology-proven chronic HP [39]. The presence of ground-glass opacities, non-honeycomb cysts or consolidation, even on an otherwise UIP-like background, should suggest alternative diagnoses other than IPF and possibly require histology confirmation. The coexistence of pleural or pericardial effusion, a dilated oesophagus or airway-associated abnormalities might be evocative of CTD-ILD [37]. Serologic testing for CTD (including rheumatoid factor, anti-cyclic citrullinated peptide and anti-nuclear antibody titre and pattern) is recommended in the majority of patients in diagnostic work-up of suspected IPF and certainly a careful assessment should be performed in younger female patients (less than 50 years of age), possibly presenting with some features of CTD such as Raynaud phenomenon, sicca syndrome or arthritis [4, 40]. Furthermore, despite a similar UIP pattern, patients presenting with a CTD-related ILD have a better prognosis as compared to patients with IPF [40, 41].

A differential diagnosis dilemma can also arise among IIPs, as NSIP may mimic a definite UIP pattern, and therefore IPF, when emphysema [42] and traction bronchiectasis coexist [7]. Similarly to radiographic abnormalities, histologic features characterizing the UIP pattern may be appreciated in other non-idiopathic conditions, such as connective tissue diseases (mainly rheumatoid arthritis), chronic hypersensitivity pneumonitis, familial pulmonary fibrosis, asbestosis, drug toxicity, or even in association with other ILD, such as features of smoking-related ILD (e.g., respiratory bronchiolitis-associated ILD or desquamative interstitial pneumonia). Thus, histology alone cannot define a UIP pattern as IPF, but requires a correlation with clinical-radiological data, including results of specific laboratory tests (e.g., autoimmunity serum markers).

Furthermore, it is important to remind that the recognition of a UIP pattern may be just a first step in labelling an interstitial lung disease and does not mean IPF by definition. In fact, an important point underlined by the pathologists involved in the 2011 evidence-based IPF guidelines [4] is the recognition of several histologic features that can be found in a background of a UIP pattern, but often secondary to other causes/disease, then excluding IPF. The presence of a UIP pattern with scattered granulomas (often with upper lobes and airway-centred involvement) likely favours a diagnosis of chronic hypersensitivity pneumonia; a marked inflammatory infiltrate with/without follicular bronchiolitis and chronic pleurisy might be indicative of un underlying collagen vascular disease (e.g., rheumatoid arthritis); a consistent eosinophilic infiltrate leads to consider a chronic drug toxicity; and the finding of asbestos bodies in a context of UIP pattern should be indicative of asbestosis (Fig. 21.3) [43–45].

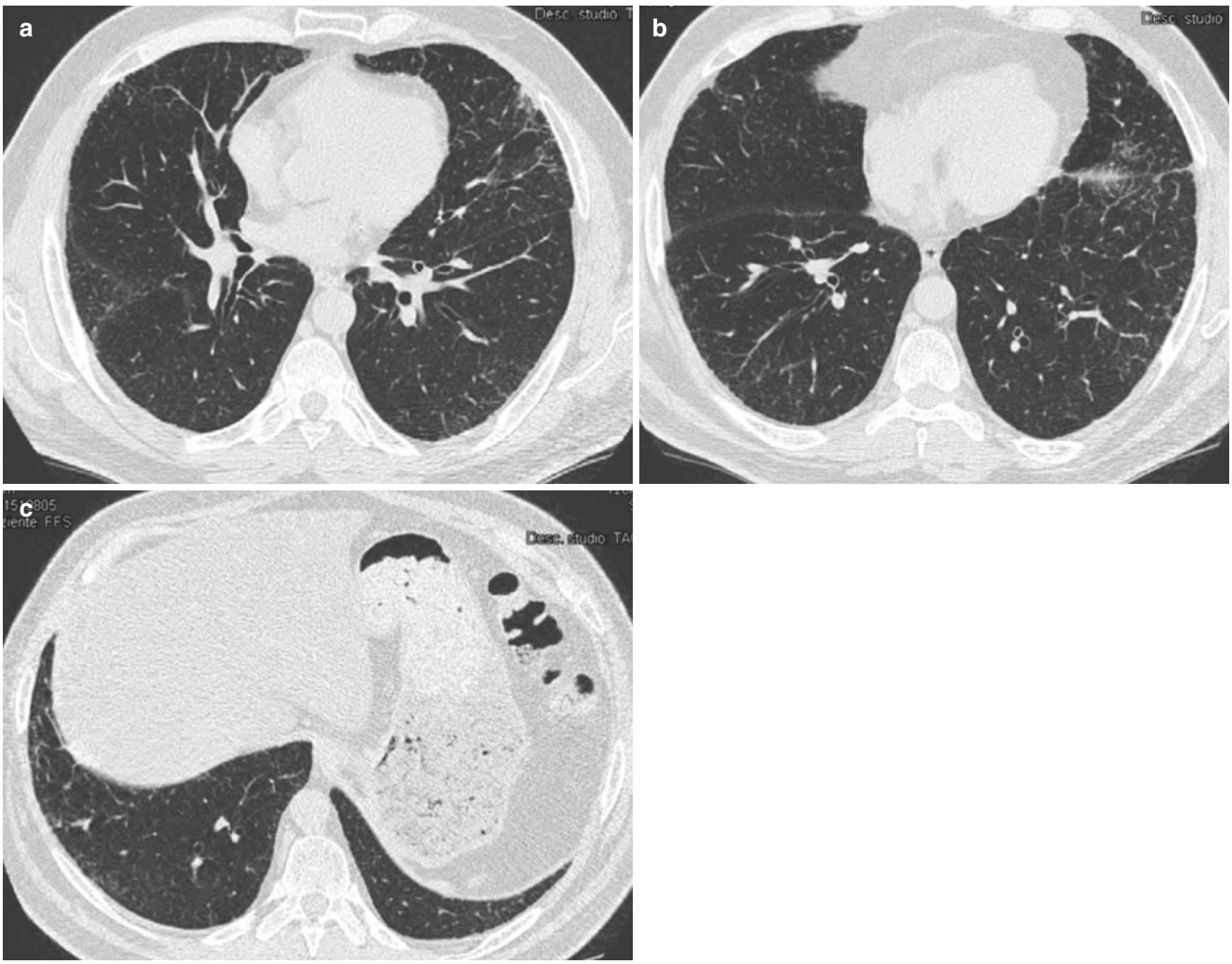


Fig. 21.4 High resolution CT scan of the chest showing subpleural basal reticular abnormalities in patient presenting with dry cough, "velcro-type" crackles and familial history of IPF

Clinical Vignette

A 66 years old male patient, never smoker with a history of chronic gastritis and a familiar history for idiopathic pulmonary fibrosis (IPF) (a younger brother died after acute exacerbation of IPF in 2008) started to suffer from persistent dry cough in 2011. Nor exertion dyspnea neither other non-respiratory symptoms were present; pulmonary function tests were normal, including diffusion capacity. Bibasilar "velcro-type" crackles were present at chest auscultation, and a high resolution CT scan of the chest showed minimal interstitial changes characterized by reticular thickening with a predominant subpleural basal distribution: no honeycomb was detectable (Fig. 21.4). In accordance with current guidelines, a surgical lung biopsy was performed. In all three specimens of lung parenchyma obtained the histopathology revealed the presence of a diffuse interstitial process with a pattern consistent with usual interstitial pneumonia (UIP) (Fig. 21.5).

This case suggests that, even in the absence of a definite UIP-like pattern at chest HRCT scan, other factors might be taken into account to refine the diagnostic suspicion of IPF. In this patient, the occurrence of IPF in a brother and the presence of "velcro-type" sounds at chest auscultation were both supportive of a diagnosis of IPF, although a confirmation by surgical lung biopsy was necessary, in accordance with the current diagnostic criteria. Even if genetic testing is not recommended at present, it is possible that the rapidly accumulating data in the field of genetics of pulmonary fibrosis will in the future contribute to the improvement of the diagnostic algorithm in these patients.

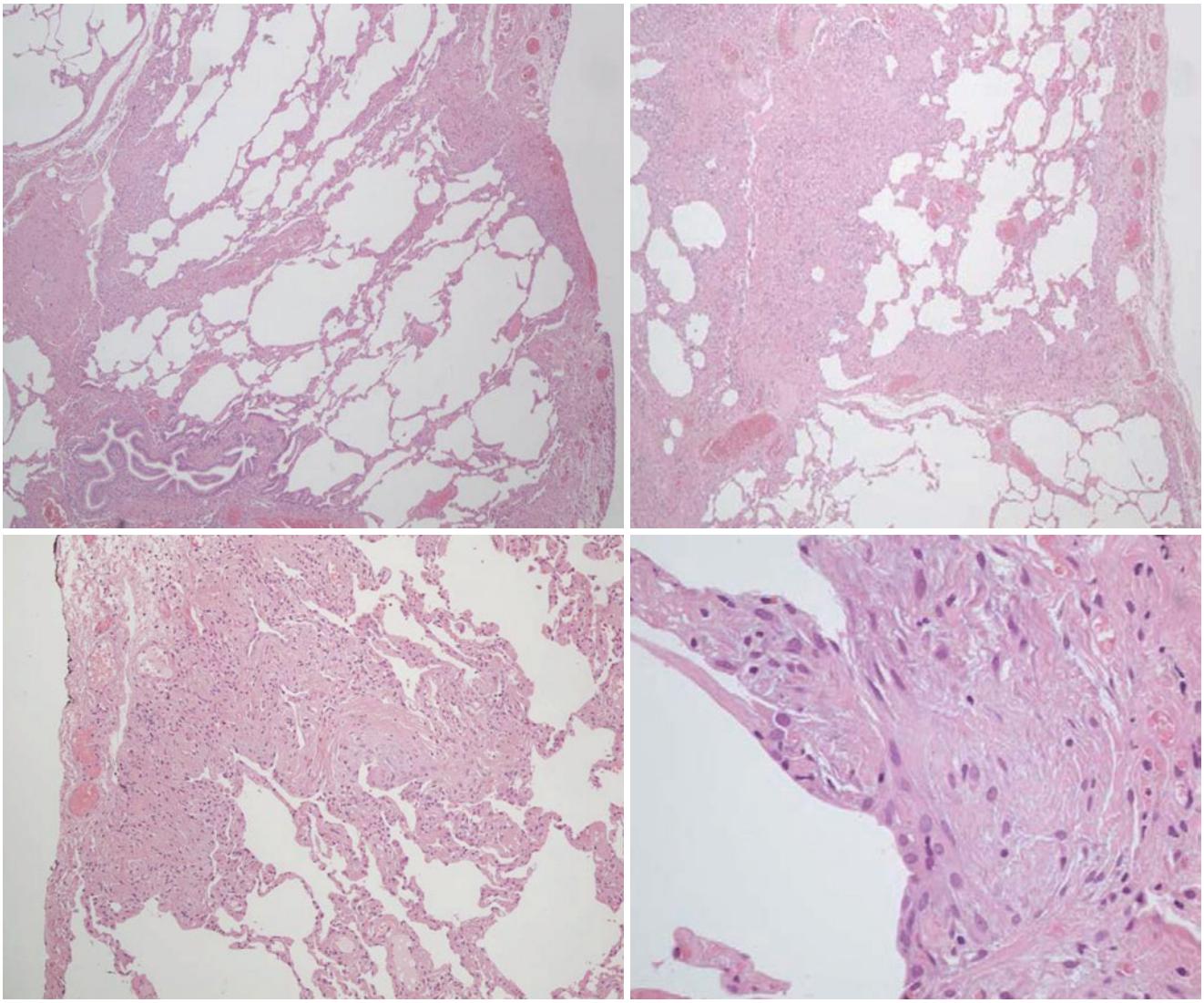


Fig. 21.5 Typical histologic features of a definite UIP pattern on surgical lung biopsy, showing architectural fibrotic distortion with spatial and temporal heterogeneity along with areas of preserved lung, microscopic honeycombing, and fibroblast foci

Box 21.1: Diagnostic Criteria

Current diagnostic criteria mainly refer to the evidence-based ATS/ERS/JRS/ALAT guidelines on diagnosis and management of IPF [4] in which a clear definition of a UIP pattern has been proposed. However, it is important to underscore that new data emerging from recent clinical trials might in the near future have an impact on these criteria. Given the high positive predictive value for a UIP pattern on HRCT, imaging has been accepted as a reliable surrogate of the surgical biopsy in at least a half of suspected IPF cases. Then, pathologists actually have to deal with more difficult cases than in the past, basically lacking honeycomb changes at imaging study.

According to different combinations of HRCT and histopathology patterns, several levels of confidence in formulating a clinical diagnosis of IPF have been suggested, as summarized in Table 21.3. These algorithms have been derived mainly from retrospective cohorts of IPF patients, while similar data are not yet available for other ILDs presenting with a UIP pattern either on HRCT or lung biopsy. The main differential diagnosis approaching non-definite UIP cases is with fibrotic NSIP. As summarized in Table 21.4, fibrotic NSIP pattern is characterized by a thickened interstitium with fibrosis and a mild inflammatory infiltrate. Fibrosis is more homogeneous both in geographic/spatial and temporal sense. The pulmonary architecture is often maintained in NSIP and fibroblastic foci are lacking, however there are cases in which a clear-cut distinction is almost impossible, possibly because of a suboptimal sampling. Another point to underline is that focal or extensive fibrosing NSIP areas may be present in UIP, both in suboptimal samples and in early-phase UIP. This fact does not necessarily suggest the existence of a continuum spectrum between fibrosing NSIP and UIP, while it is rather important to know this occurrence and that the prognosis of these cases is dictated by the UIP pattern. This may happen when biopsies are taken from multiple lobes, then evidencing UIP in one lobe and NSIP in another. Given the possibility of discordant patterns in different lobes, a diagnosis of fibrosing NSIP should be discouraged when analysing a fibrosing interstitial process on a single biopsy or when dealing with end-stage honeycomb change or scarring.

Table 21.3 Levels of confidence of a clinical diagnosis of IPF according to specific combinations of HRCT and histopathology patterns

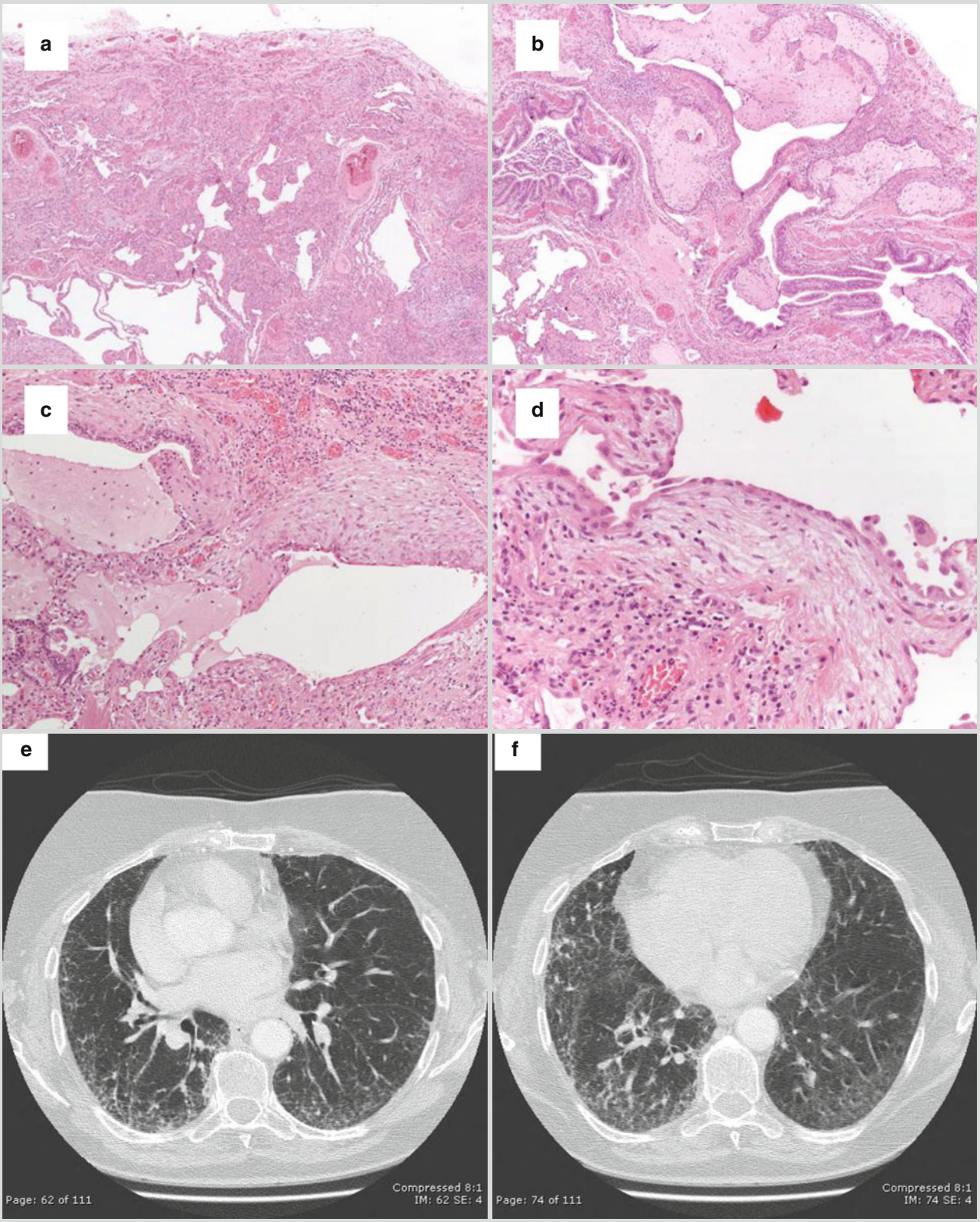
SLB pattern (if performed) / HRCT pattern	UIP	Probable UIP	Possible UIP	Non-classifiable fibrosis	Not UIP
UIP	IPF	IPF	IPF	IPF	Not IPF
Possible UIP	IPF	IPF	Probable IPF	Probable IPF	Not IPF
Inconsistent with UIP	Possible IPF	Not IPF	Not IPF	Not IPF	Not IPF

Table 21.4 Histology of UIP and NSIP patterns

	UIP	NSIP
Patchwork pattern (spatial heterogeneity)	Yes	No
Distorted architecture	Yes	No
Honeycomb	Yes	No
Fibroblastic foci (temporal heterogeneity)	Yes	No (very few)

Clinical Pathological Vignette #2

A case of IPF in a 75 years old woman with UIP pattern on histology, confirming scarred fibrosis (a, haematoxylin-eosin × 50), micro-honeycomb changes (b, haematoxylin-eosin × 100), and fibroblastic foci (c and d, haematoxylin-eosin × 150 and × 200), and possible UIP pattern on HRCT (e and f).



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The Syndrome of Combined Pulmonary Fibrosis and Emphysema

22

Vincent Cottin and Jean-François Cordier

Pulmonary emphysema and the idiopathic interstitial pneumonias, of which idiopathic pulmonary fibrosis (IPF) is the most frequent, are separate entities characterised by distinct clinical, functional, radiological, and pathological characteristics. However, recent studies have identified emphysema, among other comorbid conditions, more frequently associated with IPF than previously considered. Moreover, it has recently been better recognised that the combination of pulmonary fibrosis and emphysema potentially alters the clinical presentation and outcome.

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.

In 1990, the group headed by 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 at chest computed tomography (CT) [2], and was associated with dramatically decreased carbon monoxide transfer factor (DLco) contrasting with and preserved total lung capacity (TLC) and normal or subnormal forced expiratory volume in one second (FEV_1) : forced vital capacity (FVC) ratio. This report mostly emphasized that CT of the chest was helpful to provide with a working diagnosis in patients with severe dyspnea and subnormal spirometry.

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In 1997, Wells et al. [3] described the functional impact of emphysema in patients with "cryptogenic fibrosing alveolitis", with 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. [4] further analysed in a sophisticated approach how emphysema impacts pulmonary function in IPF, and derived a score (the "composite physiologic index", CPI) from disease extent at CT 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 a couple of isolated reports [5, 6] of observations similar to that of Wiggins et al. [2], it was not until 2005 that combined pulmonary fibrosis and emphysema (CPFE) was individualised as a distinct syndrome by the *Groupe d'Etude et de Recherche sur les Maladies "Orphelines" Pulmonaires* (GERM"O"P) [7] occurring in smokers or ex-smokers and representing more than a mere comorbid condition. CPFE was defined at chest CT 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) enlightened the high prevalence and prognostic significance of pulmonary hypertension (PH) in patients with CPFE [7].

Since then, several series of 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. 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 [8], altogether belonging to smoking-induced lung diseases [9]. Lung cancer [10] and PH may also be part of the spectrum.

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It was still unclear whether CPFE corresponds to the coincidental association of IPF and emphysema by chance, or to a genuinely unique entity. Much remains to be learned about the pathophysiology of this syndrome, diagnostic boundaries with IPF, and management. However, it clearly presents with a characteristic clinical and especially functional profile, with an increased risk of precapillary PH associated with a poor outcome. The clinical and functional characteristics of CPFE, and its relevance for clinical care, monitoring of patients, and trial design, therefore fully justify its individualisation as a syndrome [11].

Epidemiology and Etiologies

Tobacco Smoking and Male Sex

Emphysema has been reported in 21–33 % of patients with IPF [6, 12–18], most of whom are current or past tobacco smokers. A lower prevalence (8 %) was found in recent series from the USA [18], likely accounting for the lesser use of tobacco in this population. Differences in the prevalence of emphysema between studies account for different tobacco use in various countries, and for the definition used for emphysema. Tobacco smoking is by far the predominant etiology of the CPFE syndrome, with a smoking history present in 98 % of patients [19], and a mean tobacco history of about 40 pack-years [7, 10, 20, 21]. Interestingly, exposure to tobacco smoke may cause both fibrosis and emphysema in an animal model [22]. A comprehensive review of common and distinct mechanisms between IPF and chronic obstructive pulmonary disease can be found elsewhere [23].

CPFE associated to tobacco smoking in the absence of any other potential etiologic factor has a 9:1 male:female ratio [19]. Both IPF and emphysema also separately predominate in males [24–27], although with lesser predominance. It is not known whether the male predominance of the CPFE syndrome is only related to the higher prevalence of tobacco smoking in men, or to the link between tobacco smoking and both emphysema and IPF. Smoking rates in men versus women generally tend to become similar in western countries, and likely do not explain the totality of the gender difference in CPFE. 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.

Genetic Predisposition

It has been postulated [11] that a genetic background may predispose a subset of smokers to develop the typical syndrome of CPFE, in a similar way as smoking preferentially increases the risk of emphysema or IPF depending on largely unknown factors but likely involving lung aging and senescence [23, 28–30]. Potential genetic predisposition to CPFE is only beginning to be explored, with only few cases reported of mutations carrying a Mendelian risk of CPFE or IPF. However it is likely that CPFE may result from genetic predisposition in combination with tobacco smoking or exposure to other aerocontaminants or risk factors. Identifying gene mutations that render individuals vulnerable to CPFE would represent a big step into the understanding of its pathophysiology. Importantly, epigenetic alterations may be equally important as genetic mutations [31].

The CPFE syndrome was reported in a patient with familial ILD carrying a mutation in the surfactant protein C gene [32]. Typical CPFE was found in a 41-year-old non-smoker patient with mutation in the *ABCA3* gene [33]. Some "emphysema-like" lesions were further observed in patients with familial (genetic) IPF with mutations in the surfactant protein C gene [34, 35] or in the telomerase complex [36, 37]. As telomere length is reduced both in COPD and IPF patients, telomeres are expected to be shorter than normal in patients with CPFE [11, 19], which requires further study [38]. Interestingly, 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 [39]. As observed in familial pulmonary fibrosis (without emphysema), mutations in surfactant or telomerase genes when present in a family can be associated with a diversity of pathologies, especially UIP and NSIP. Incidentally, scattered cystic lesions and ILD with mostly ground-glass attenuation can be observed in patients with neurofibromatosis, however not reproducing an imaging pattern similar to that of (tobacco-related) CPFE syndrome [40].

Gene mutations that may predispose specifically to develop emphysema have not been explored. It is known that distinct mutations can increase the susceptibility to different phenotypes of emphysema. In a recent study, centrilobular emphysema was associated to single nucleotide polymorphims in the *MMP9* (metalloprotease-9) and *TGFβ1* (coding for transforming growth factor-β-1), whereas paraseptal emphysema and/or airflow obstruction were associated to single nucleotide polymorphims in *TIMP2* (tissue inhibitor of metalloprotease-2) and *TNF* (tumor necrosis factor) [41]. Although preliminary, these results shed light on mechanisms

of different emphysema subtypes and are relevant in the setting of the CPFE syndrome.

Systemic Diseases

The CPFE syndrome may occur in virtually any of the connective tissue diseases, with no clear difference in presentation according to the systemic disease or auto-antibody type [42]. 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 high resolution (HR) CT was 23 % in patients with ILD associated to connective tissue diseases and 44 % in patients with IPF ($p=0.05$) [43]. 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 account for this difference [44].

In a study of 34 patients with typical CPFE occurring in connective tissue diseases [21], the predominant underlying diseases were rheumatoid arthritis (Fig. 22.1) and systemic sclerosis (Fig. 22.2) (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 [21]. The onset of a CPFE syndrome before the occurrence of the connective tissue disease is very rare [21].

In 150 consecutive patients with rheumatoid arthritis [45], 19 % had ILD, 15 % had so-called "emphysematous bullae", including 8 % (12 out of 150) who had both ILD and emphysema. Emphysema was observed in 24 % of 63 patients with rheumatoid arthritis and ILD [46], and was significantly more frequent among patients with a CT 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 at chest CT in 48 % of ever-smoker patients with rheumatoid arthritis and ILD, and in 35 % of ever-smoker patients with IPF, despite median

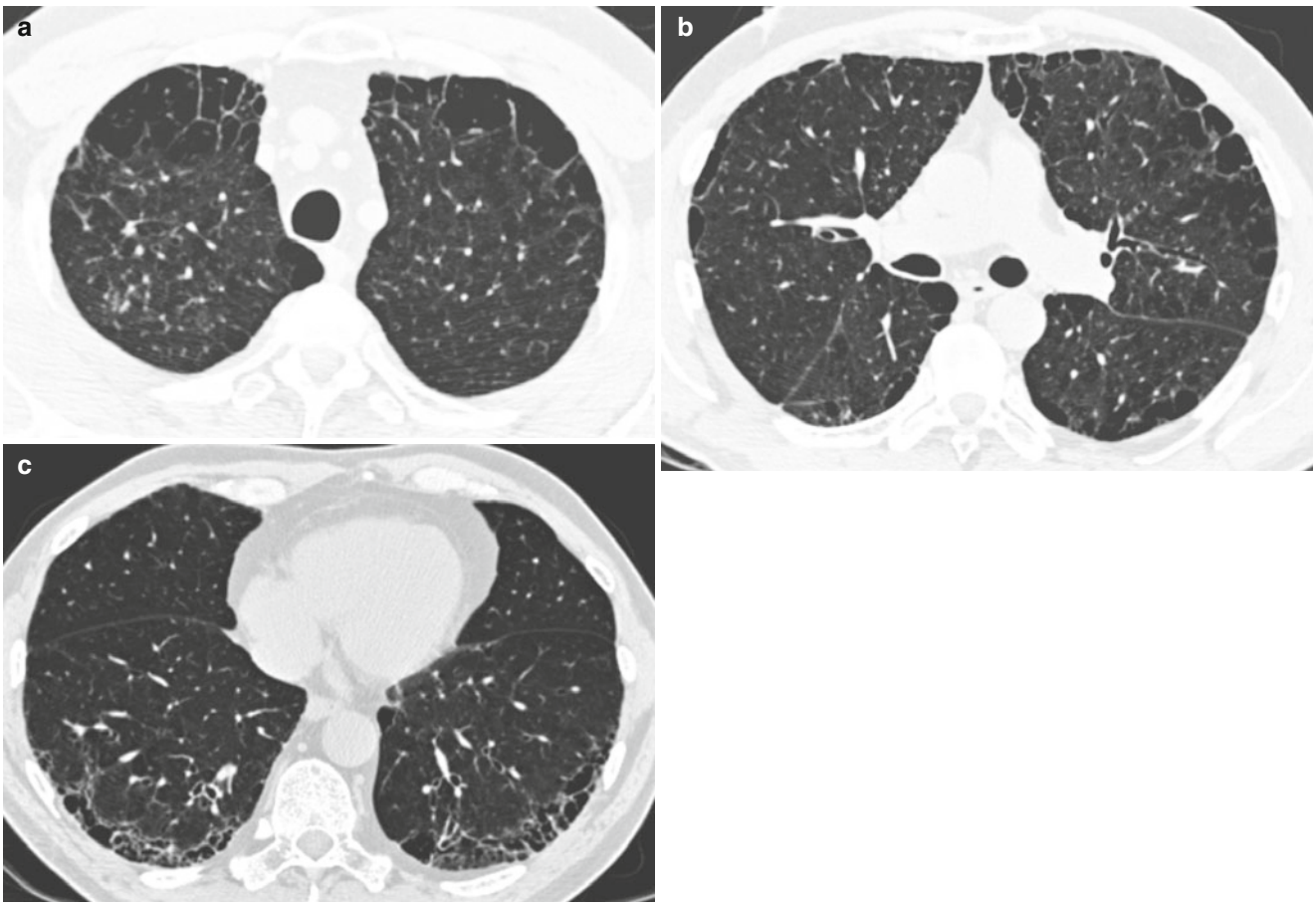

Fig. 22.1 CPFE syndrome at chest CT in a patient with rheumatoid arthritis (male, smoker). (**a**) upper lobes showing centrilobular and paraseptal emphysema; (**b**) mid regions of the lungs, showing predominantly paraseptal emphysema, with thickening of the interlobular septa; (**c**) lower zones showing usual interstitial pneumonia pattern with reticulation, honeycombing, and traction bronchiectasis

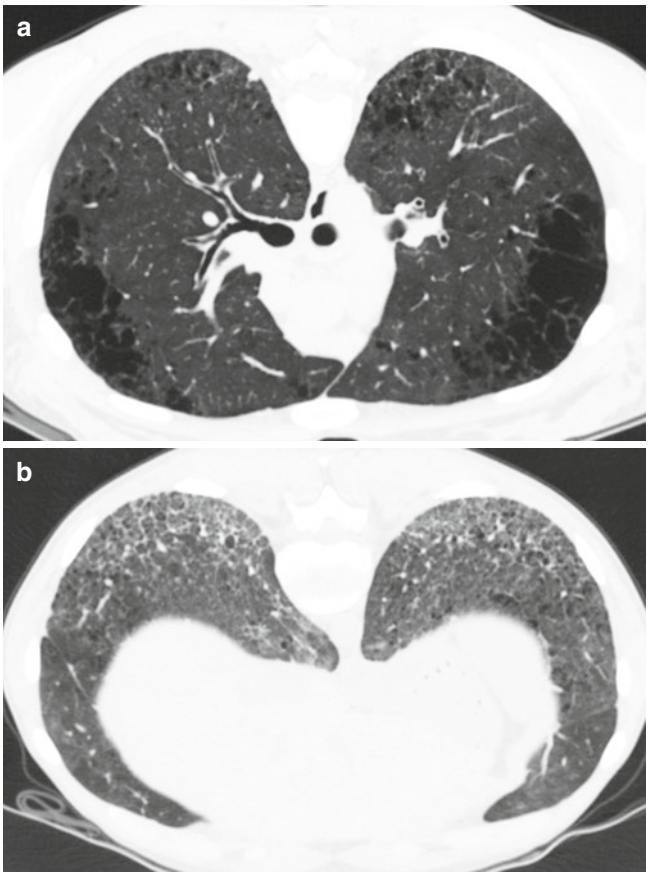

Fig. 22.2 CPFE syndrome at chest CT in a 28-year old female patient with severe systemic sclerosis and high-titer anti-U1-RNP autoantibodies, with a smoking history of less than 5 pack-years. (**a**) Upper lobes demonstrating centrilobular and paraseptal emphysema; (**b**) lower zones showing nonspecific interstitial pneumonia pattern with reticulation, ground-glass opacities, and mild traction bronchiectasis

smoking histories of less than 25 pack-years in both cohorts [47]. 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 (the human leukocyte antigen DRB1 shared epitope) with environmental exposures (especially tobacco smoking) and autoimmunity (anti-cyclic citrullinated peptide antibodies) is now well established [48]. Briefly, tobacco smoking is responsible for inflammation and citrullination of proteins within the lung, a post-translational modification that alters L-arginine residues into L-citrulline residues through peptidyl arginine deiminase, thereby altering protein folding and charge, with enhanced degradation by proteases, and exposure of cryptic epitopes, which in turn increases the risk of developing anti-cyclic citrullinated peptide auto-antibodies produced in the lung, and then rheumatoid arthritis [49]. In this process, the immune response developed against modified self-proteins transfers inflammation from the lungs to the joints [50]. Tobacco smoking increases the incidence and severity of rheumatoid arthritis [51], with furthermore a higher risk of developing extra-articular complications [52] possibly including ILD [53, 54]. The ILD may exacerbate in patients with CPFE and rheumatoid arthritis, occasionally upon drug therapy [55]. 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 [56].

CT evidence of emphysema was found in 8.4 % of 225 patients with systemic sclerosis [57], 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 sclerosis [58]. Emphysema is more prevalent in systemic sclerosis patients with pulmonary fibrosis than in control smokers with connective tissue disease or IPF, after adjustment for the smoking history [59]. The CPFE syndrome may occur in patients with only mild smoking history [60, 61], suggesting that systemic sclerosis itself might contribute to the development of emphysema, a hypothesis that remains to be explored. Spontaneous emphysema and right heart hypertrophy develop spontaneously in tight-skin mice that harbor a duplication in the *fibrillin-1* gene and resemble human systemic sclerosis [62, 63]. Modulation of inflammatory markers in animal models [64–69] supports the hypothesis that the connective tissue disease *per se* may play a role in the pathogenesis of the CPFE syndrome, possibly through chronic inflammation or epigenetic dysregulation (post-translational modifications of histone proteins and hypermethylation) [70, 71].

CPFE has been reported in patients with polymyositis, Sjögren's syndrome, mixed connective tissue disease, overlapping connective tissue disease, with consistent antibody profiles [21]. Emphysematous changes were found in 3 of 65 autopsy cases of polymyositis/dermatomyositis [72]. Tobacco smoking also increases the risk of developing systemic lupus erythematosus [73], however CPFE seems rare in lupus.

The CPFE syndrome may occur in patients with so-called interstitial pneumonitis with autoimmune features (also referred to as ILD in undifferentiated connective tissue disease [74], auto-immune featured connective tissue disease [75] or lung-dominant connective tissue disease [76]), e.g. the recently individualised condition with manifestations suggestive of connective tissue disease but not satisfying the criteria of any defined disease entity [77]. 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 [78].

The CPFE syndrome may also develop in patients with systemic vasculitis especially microscopic polyangiitis [79]. 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 [80]. 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 to disease pathogenesis.

Other Etiological Contexts

CPFE has been occasionally reported in subjects with exposure to agrochemical compounds [81], coal dust [82, 83], talc [84], or to rare earth elements and tobacco [85]. In addition, CPFE was reported in patients with asbestosis [12, 13, 86, 87], silicosis [88], and sarcoidosis [89], occasionally in the absence of tobacco smoking. Subjects exposed to mineral dust and especially coal dust may develop emphysema and pulmonary fibrosis simultaneously [19]. The combination of emphysema and ILD has been further reported in the setting of farmer's lung [90, 91].

Clinical Manifestations

Patients with the CPFE syndrome have a mean age of 65–70 years [7, 19], with younger individuals especially in those with connective tissue disease or genetic predisposition to ILD (See Clinical Vignette). The male:female ratio is greater than 9:1 in CPFE, with 60 men and only 1 woman in the seminal series [7]. 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 contrast with the female predominance found in series of patients with connective disease and ILD (without emphysema) [92].

Patients with CPFE usually report severe dyspnea at exercise [2, 6, 7, 14, 17, 18, 20, 21, 81, 93–95]. 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 [21].

Clinical Vignette

A 68-year old male, ex-smoker, with a history of 48 pack-years, who had worked as a mason, with no significant exposure to asbestosis, 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 CT 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. 22.5). Areas of admixed pulmonary fibrosis and emphysema were observed in the mid sections of the lungs. 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 possible UIP pattern at CT. Lung biopsy was not performed. Inhaled bronchodilators were initiated. Fourteen months later, he was readmitted for acute right heart failure. Right heart catheterisation 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 5 months after the diagnosis of pulmonary hypertension from acute respiratory failure.

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 [19, 21]. Spirometric values and lung volumes are preserved, or with FVC, TLC, and/or FEV_1:FVC close to the lower limit of normal. In our 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 [20], lung volumes were comparable with FVC of 88 ± 18 % of prediced, however DLco was only 24 ± 14 % and Kco was 28 ± 16 % of predicted.

Merged data from three study populations [7, 20, 21] 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 2009 stage 0 (FEV_1:FVC ≥0.70 and FEV_1 ≥80 % of predicted) and further 22 % were unclassified according to GOLD 2009 (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 [96]. 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 associated to the elastic forces increased by pulmonary fibrosis (with presumably increased elastic recoil, as well as prevention by traction forces of expiratory airway collapse), and the effects of the obstructive physiology with propensity to hyperinflation due to emphysema. This is illustrated by the possibility of FEV_1:FVC to actually improve back to normal values while the disease progresses, with worsening of dyspnea and DLco [97]. The annual change in FEV_1:FVC has been shown to moderately increase in patients with CPFE, as compared to a more profound annual decrease in those with chronic obstructive pulmonary disease [98]. 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 [99]. 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 pseudonormalisation of lung mechanics in CPFE [100]. Conversely, both disease components concur to reduced alveolar capillar 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 our series of 61 patients [7], 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 oxymetry decreased by 9 ± 6 %. In another group of patients with CPFE and PH, the arterial oxygen saturation measured by pulse oxymetry decreased by 15 ± 8 % [20]. Hence, exercise limitation with decrease in oxygen saturation, and isolated [101] and/or severe [102] reduction in DLco or Kco contrasting with mild ventilatory defect or 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 [3, 18, 103, 104]. 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) [103, 104]. 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 [18]. Demographics of CPFE and IPF are similar in those studies, however patients with CPFE tend to have greater tobacco smoking history [18, 103]. 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 transfer capacity [98].

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 [103, 105]. Therefore, changes in FVC and DLco are not reliable indicators of disease progression in patients with CPFE. As most recent clinical trials in IPF use FVC as an endpoint, it is preferable that patients with CPFE be excluded from IPF trials [11], and similarly from trials of ILD in connective tissue disease [42]. In clinical practice, serial changes in FVC and DLco are used to monitor disease progression in IPF [27], 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 [17]; FEV_1:FVC might also be useful [106]. Whether these observations are useful in the clinic awaits further evaluation.

Imaging

Chest radiograph may show hyperlucency of the upper zones of the lungs, and diffuse parenchymal infiltrates in the lower lobes (Fig. 22.3). HRCT of the chest has dramatically enhanced the recognition of CPFE and is key to the diagnosis. Patients with CPFE present with both emphysema (generally predominating in the upper lobes) and features suggestive of pulmonary fibrosis (mostly in the lower lobes), with occasionally lung pathology available.

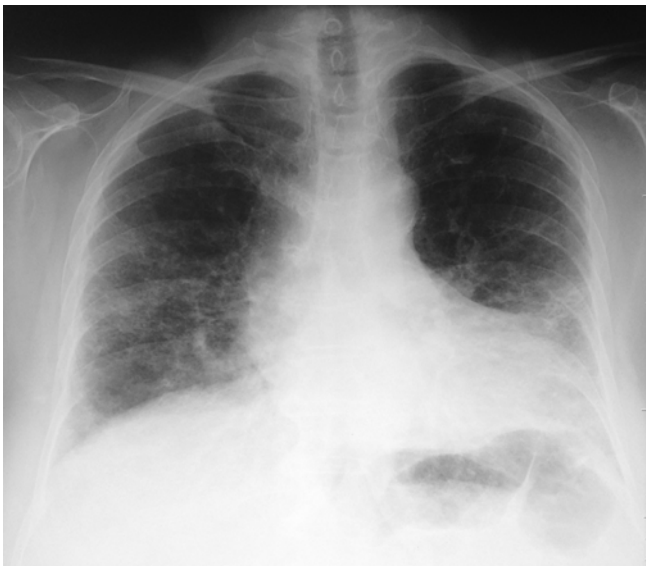

Fig. 22.3 Chest radiograph of CPFE syndrome showing hyperlucency of the upper zones of the lungs, and diffuse parenchymal infiltrates in the lower lobes (male, smoker)

Computed Tomography Characteristics

In our series [7], 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 was present in two-thirds of the patients. Some degree of centrilobular emphysema was present in 97 % of the patients [7, 81]. In addition, paraseptal emphysema present in 93 % of patients with CPFE represented the predominant type of emphysema in more than half of patients [7]. Importantly, paraseptal emphysema seems to be more frequent in CPFE than in chronic obstructive pulmonary disease [93], and may actually be considered a hallmark of the syndrome [11, 81]. Panlobular emphysema is seldom observed. Signs 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 [21, 42]. 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 one mm thick. They may be associated or not with typical honeycombing, from which they differ by the larger size of the cysts and their often being not clustered, whereas honeycombing corresponds to clustered, cystic air spaces, 3–10 mm and up to 2.5 cm in diameter [107]. They may be associated with more extensive emphysema at imaging [108]. 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 [99, 109]. Enlargement over time of thick-walled large cysts has been described [108]. We consider that they are one typical feature of the CPFE syndrome [21].

Imaging Phenotypes

Due to the high heterogeneity of imaging in patients with CPFE, attempts were made to identify distinct imaging phenotypes [99] 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. 22.4); (2) progressive transition from emphysema lesions to fibrosis, with significant overlap or admixture in mid areas (Fig. 22.5); (3) conspicuous paraseptal emphysema with predominant subpleural bullae/cysts with thickened walls (Fig. 22.6). The pattern of thick-walled large cysts (Fig. 22.7), described more recently [21], may overlap with that of predominant paraseptal emphysema. In addition, a number of observations do not fit into one of the above categories [99]. 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 [99]. However, whether these subgroups have physiological relevance, and whether the pattern of predominant paraseptal emphysema really is the most associated with preserved spirometry, as shown in patients with chronic obstructive pulmonary disease [110], warrant confirmation.

Imaging Patterns

A majority of patients have a HRCT pattern of UIP (Figs. 22.1, 22.4, and 22.5) [7], however other patterns have been reported on imaging and/or histopathology [7, 111–114]. Similarly, mild to moderate ground glass attenuation is more prevalent in CPFE than in typical IPF patients [7], likely corresponding to NSIP (Fig. 22.2) [113] or to various smoking-related ILDs such as desquamative interstitial

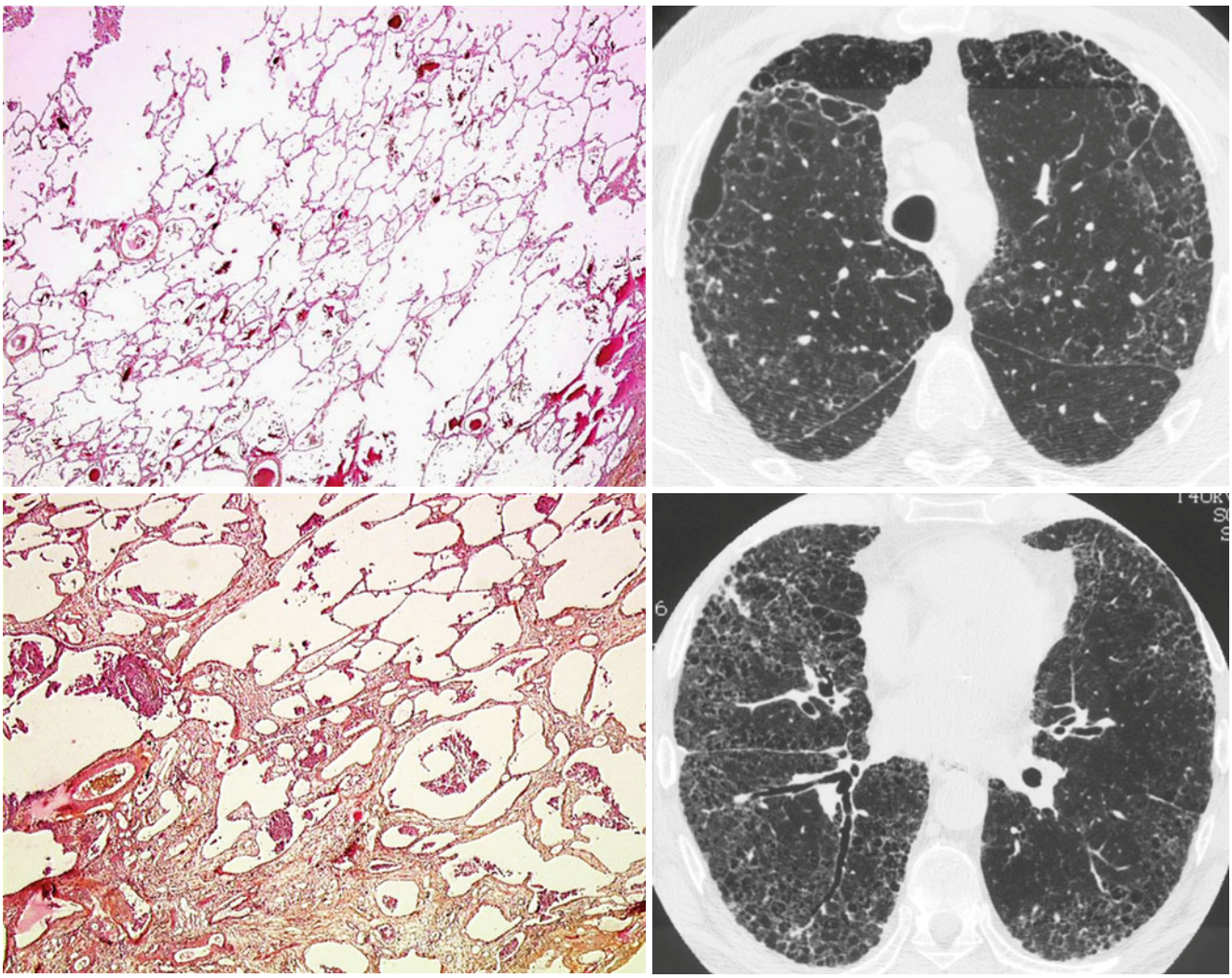

Fig. 22.4 CPFE syndrome with centrilobular emphysema and usual interstitial pneumonia (male, smoker). *Upper left panel*: lung biopsy in right upper lobe showing centrilobular emphysema; *upper right panel*: chest CT at the level of the trachea showing moderate centrilobular emphysema, along with reticular 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 CT 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))

pneumonia [111] or respiratory bronchiolitis-associated ILD. Therefore, not all patients with (tobacco-related) CPFE have IPF [11], and not all patients with CPFE in the setting of connective tissue disease have a pattern of UIP [21].

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 [113], with small thick-walled cystic changes, may falsely resemble honeycombing at HRCT [114], a situation sometimes coined "possible honeycombing" [115]. Presence of emphysema is one of the main reasons for disagreement between radiologists in the CT assessment of honeycombing [116]. Because the recent international criteria for the diagnosis of IPF [117] are largely based on HRCT imaging and especially the presence of honeycombing (in patients without a lung biopsy), 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 (at least two rows) in honeycombing that predominates in the lung bases [118].

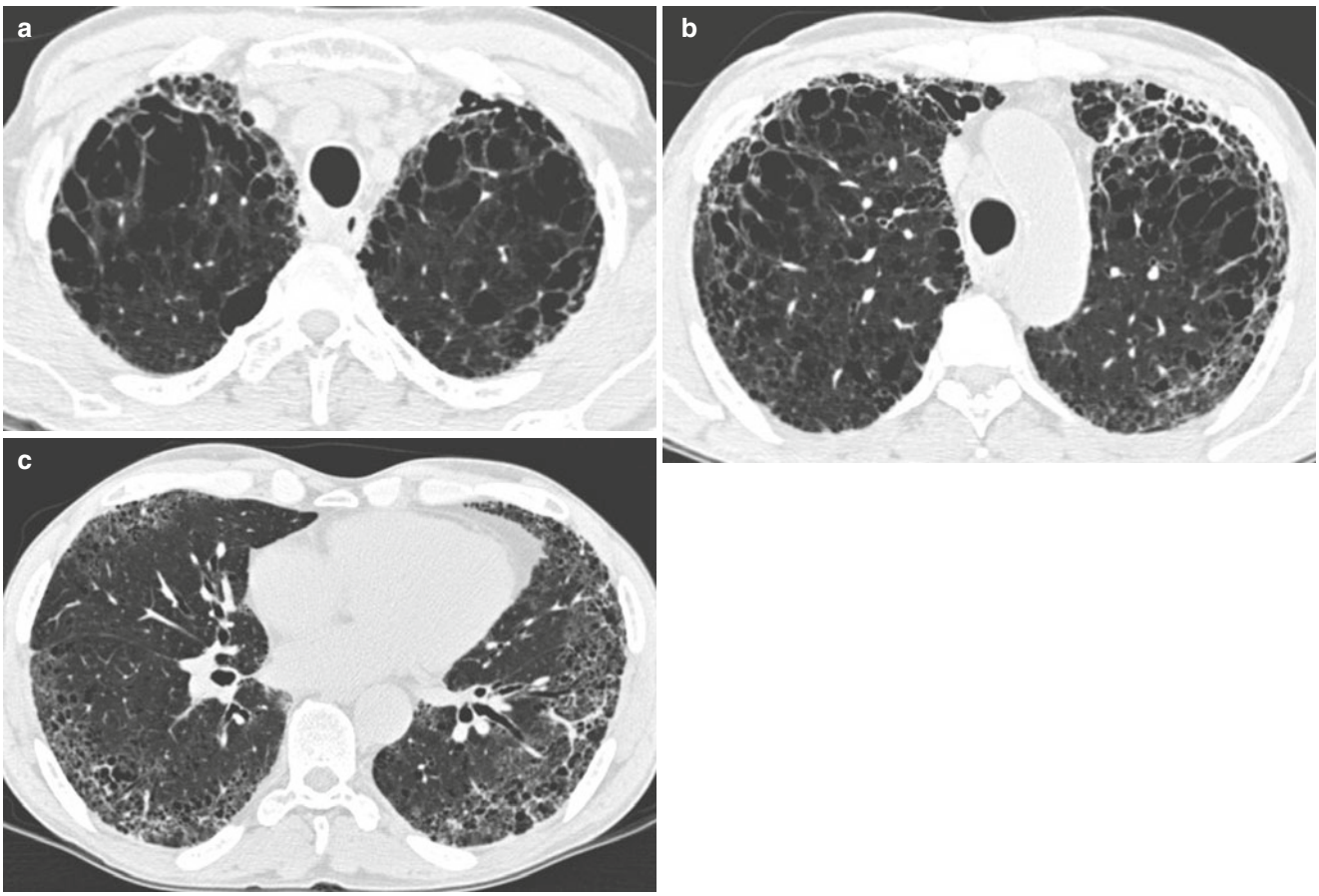

Fig. 22.5 CPFE syndrome at chest CT with centrilobular emphysema and usual interstitial pneumonia pattern, progressive transition phenotype (male, smoker). (**a**) Upper lobes showing centrilobular emphysema predominantly in anterior areas, with thickening of the interlobular septa; (**b**) mid regions 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

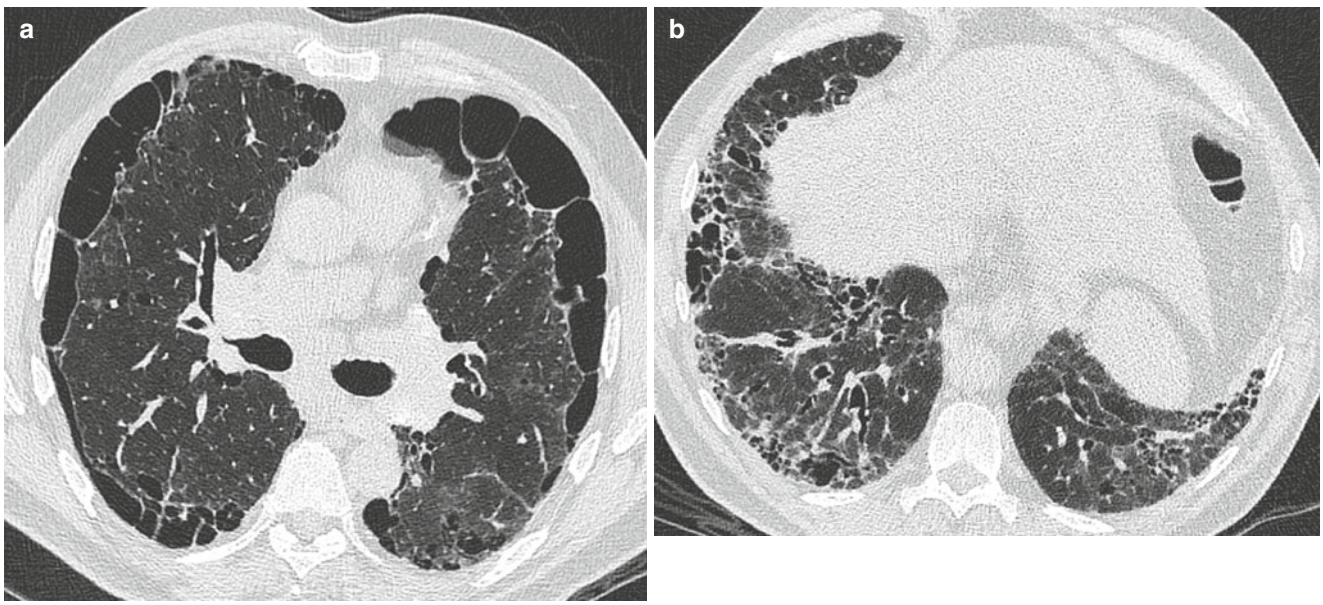

Fig. 22.6 CPFE syndrome at chest CT with predominantly paraseptal emphysema (male, smoker). (**a**) Mid Zones lobes showing predominantly paraseptal emphysema, with mild thickening of the interlobular septa; (**b**) lower zones showing fibrotic changes with honeycombing, traction bronchiectasis, and reticulation, predominating in the right lower lobe

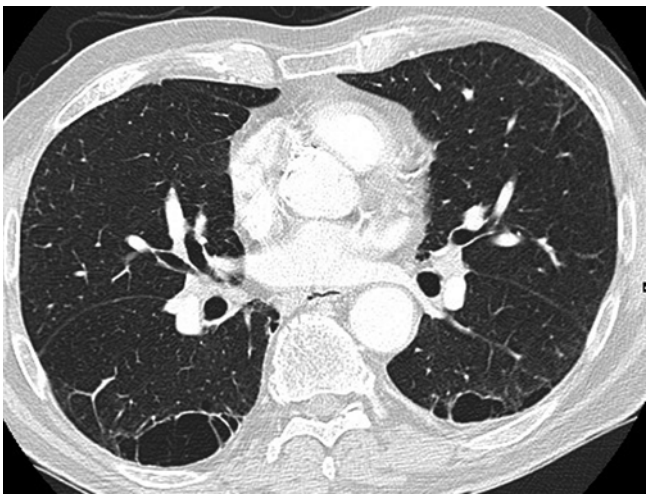

Fig. 22.7 Chest CT showing thick-walled large cysts (male, ex-smoker). In this example, large subpleural cysts are relatively isolated, with little reticulation in the area surrounding the cysts. Septa are visible inside the right lower lobe cyst

Table 22.1 Working diagnostic criteria for the syndrome of combined pulmonary fibrosis and emphysema (CPFE)

1. "Conspicuous" emphysema (centrilobular and/or paraseptal) at HRCT defined as well-demarcated areas of low attenuation delimitated by a very thin wall (≤1 mm) or no wall[a,b]
2. Bibasilar reticular abnormalities with basal and subpleural predominance, traction bronchiectasis and/or honeycombing on HRCT scan[b,c]
3. Relatively preserved lung volumes and airflow with strongly decreased carbon monoxide transfer factor[d,e]

Notes

[a]Emphysema may be semi-quantified as moderate (notable or equivalent in extent to the fibrosis) or severe (the predominant abnormality) [17]. Patients with mild (scant) emphysema typically do not present with the typical functional profile and therefore are not classified as having CPFE syndrome

[b]These may be replaced by thick-walled large cysts greater than 2.5-cm in diameter ("CPFE, thick-walled large cysts variant")

[c]Caution must be exerted for the identification of honeycombing in patients with associated emphysema. Ground-glass attenuation may be present. The HRCT pattern is usually that of UIP or possible UIP [117]; a HRCT pattern of NSIP is also possible

[d]Especially in patients with mild imaging abnormalities

[e]The presence of precapillary pulmonary hypertension in a patient with suspected CPFE may be considered as an additional clue to the diagnosis

Diagnosis of the CPFE Syndrome

Although consensus diagnostic criteria have not yet been formally established, the CPFE syndrome is currently diagnosed on the presence of both emphysema (generally predominating in the upper lobes) and features suggestive of pulmonary fibrosis (mostly in the lower lobes on imaging), with occasionally lung pathology available.

However, it is unclear what extent of emphysema and fibrosis at imaging is needed to classify an individual has having CPFE rather than lone IPF (or emphysema with no significant ILD). The following diagnostic criteria used in the seminal description of the CPFE syndrome and later series [7, 20, 21] 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 [7, 20, 21].

Other studies have 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") [17]; 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) [100]; or IPF with >10 % of the lung affected with emphysematous changes [16]; or IPF with total emphysema score ≥10 % [18], a thresholds that corresponds to GOLD stage II or worse in patients with isolated chronic obstructive pulmonary disease; etc.

Provisional diagnostic criteria for the CPFE syndrome are listed in Table 22.1 [42]. The role of multidisciplinary discussion has not been formally studied in CPFE but is likely as important as in IPF (or more) [117]. Work in progress will likely refine diagnostic criteria for CPFE based on imaging as well as on lung physiology. 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 [96, 119, 120], as described for IPF.

Biology

As in IPF and as observed in the general population, a minority of patients may have anti-nuclear antibodies, which in the absence of systemic clinical features have limited clinical relevance. As discussed above, anti-neutrophil cytoplasmic antibodies may also be found [80]. The serum levels of KL-6 (Klebs von der Lungen-6) and SP-D (surfactant protein-D) are elevated [121].

The differential cell count of bronchoalveolar lavage fluid is similar in CPFE to that of IPF and does not contribute significantly to the diagnosis [7, 71]; 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 [71] and may contribute to the development of emphysema.

Pathology

Due to emphysematous changes, frequent comorbidities, and severity of gas exchange impairment, very few patients with typical 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. A variety of pathology patterns of ILD has been reported, including predominantly a UIP pattern (Fig. 22.8), NSIP, desquamative interstitial pneumonia (with extensive fibrosis), respiratory bronchiolitis – associated ILD [7, 19, 111–113, 122]. 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 [108]. 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, occasional fibroblastic foci, surrounded by honeycombing and normal alveoli. Thick-walled large cysts were

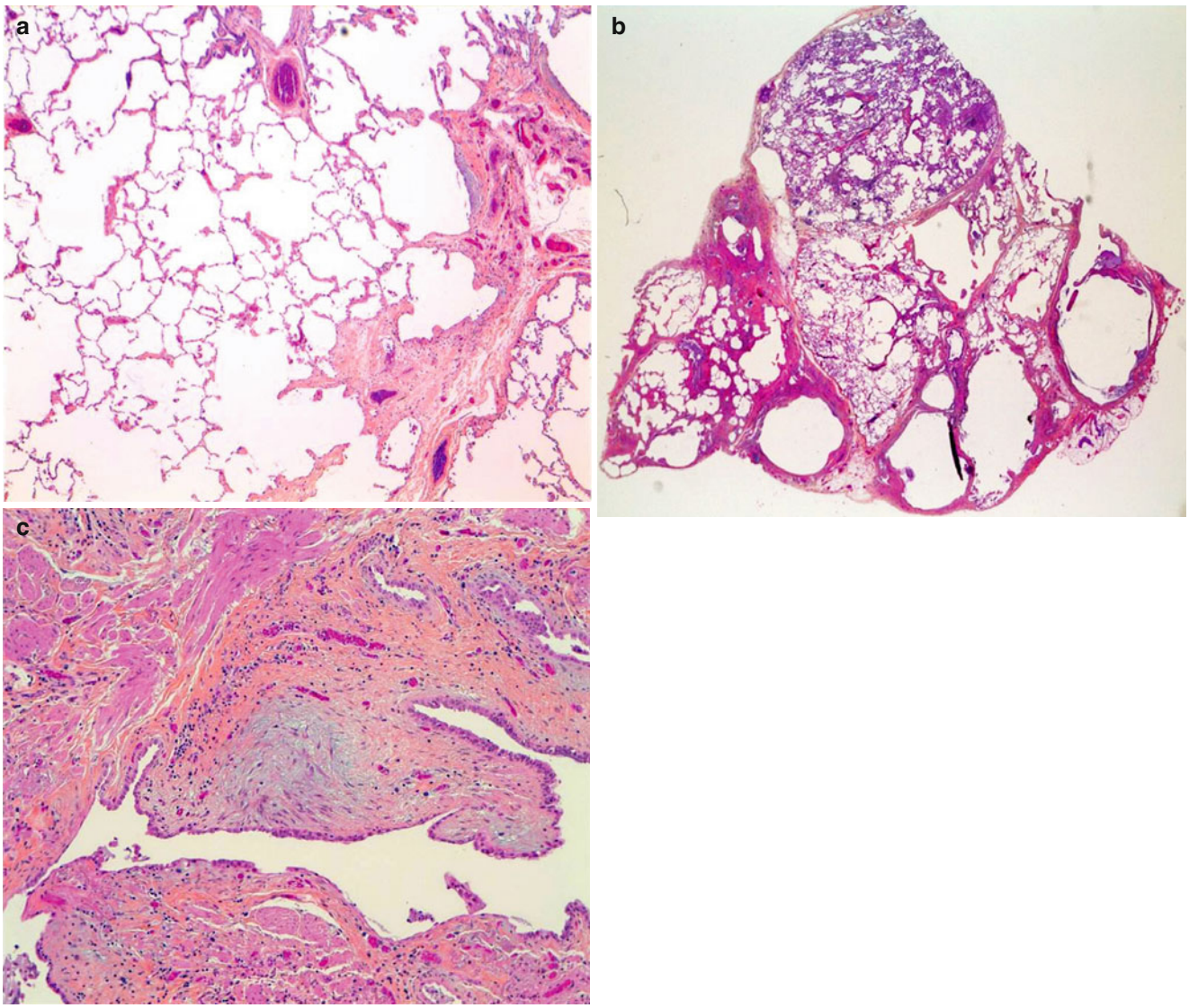

Fig. 22.8 Lung pathology in a patient with the CPFE syndrome. (**a**) Emphysema adjacent to interstitial fibrosis (upper right lobe); (**b**) dense fibrosis with subpleural pathological honeycombing (lower right lobe, low magnification); (**c**) fibroblastic focus in an area of dense fibrosis, at the center of the slide (lower right lobe, high magnification) (Courtesy of Pr Françoise Thivolet-Béjui, Lyon (France))

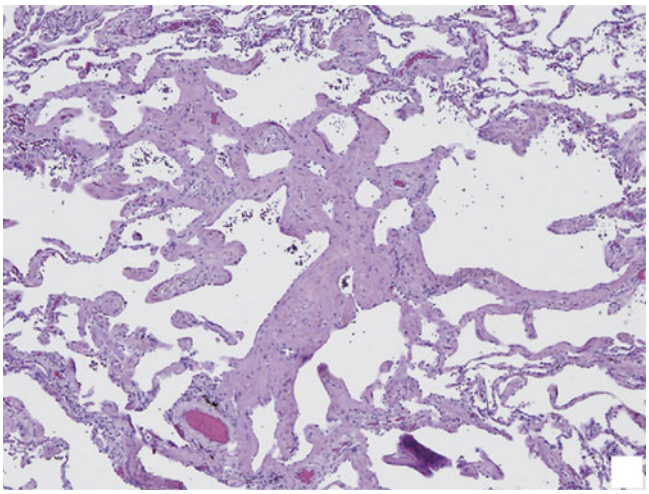

Fig. 22.9 Smoking related interstitial fibrosis. Severe interstitial fibrosis involving deep parenchyma in a centrilobular distribution associated with emphysema. Very little inflammation is present (From Katzenstein et al. [124], figure 2, panel B, with permission)

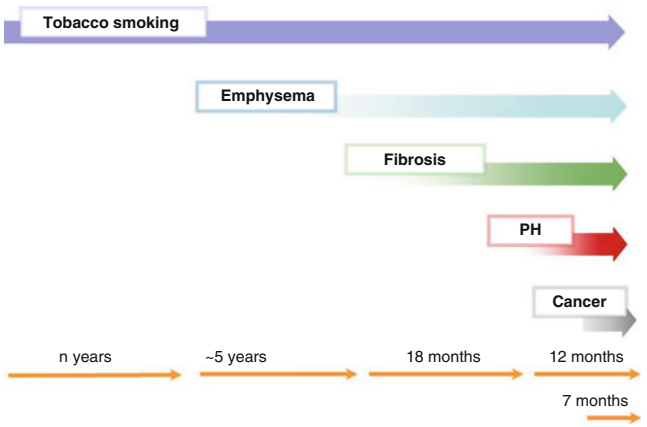

Fig. 22.10 Temporal Diagram of the main complications in tobacco-related CPFE syndrome. The median delay between emphysema and fibrosis is 5 years, and pulmonary hypertension may occur after a median of 18 months after the diagnosis of CPFE. Patients may die after a median of about 1 year from the diagnosis of pulmonary hypertension and a median of 7 months from the onset of lung cancer, with great inter-individual variability. *PH* pulmonary hypertension

not observed in IPF without emphysema [108]. Non-prominent bronchiolocentric fibrosis was occasionally present.

In addition, admixture of emphysematous changes and localized fibrosis with especially thickening of alveolar walls with little if any inflammation, and/or respiratory bronchiolitis, seems to be common in patients with CPFE. Histopathology of lung specimen in patients with emphysema has demonstrated thickened interstitium in addition to enlargement of alveolar spaces [123]. Excess of collagen and elastin deposition was present in the interstitium at electron microscopy, especially in septal walls of diseased areas [123]. Clinically occult interstitial fibrosis is surprisingly common in lobectomy specimens in smokers [124]. These abnormalities have been described with various terminologies with likely overlapping features [125]: "smoking related interstitial fibrosis" (Fig. 22.9) [126], "clinically occult interstitial fibrosis" [124], "airspace enlargement with fibrosis" [127], "fibrosis superimposed on emphysema" [125], "respiratory bronchiolitis-associated ILD" [128], "respiratory bronchiolitis-associated ILD with fibrosis" [122], and unclassifiable smoking-related interstitial fibrosis [124]. Such histopathological changes may only rarely be associated with physiological or radiological features of an ILD [125]. 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" [125].

Collectively, these 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 at pathology on one hand, and overt CPFE syndrome on the other hand, may be part of a continuum of smoking-related lung disease.

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 [7], and a dismal prognosis. PH may occur in about half of the cases after a median of 18 months following the diagnosis of CPFE [20] (Fig. 22.10). 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 [10]).

Mortality

The overall median survival in CPFE is comprised between 2.1 and 8.5 years [7, 14–16, 18, 103, 129–131]. In CPFE and connective tissue disease, the overall survival was 100 % at 1 year, 94 % at 2 years, and 73 % at 5 years [21]. 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.

Comparison of survival between patients with CPFE and IPF has been controversial [130], as results may vary according to: (1) diagnostic criteria for CPFE, with survival in CPFE possibly confounded by patients with pathology patterns 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 [129]; (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 [130], which may explain why fibrosis and emphysema are inversely correlated at the diagnosis of CPFE [105]; (4) the method used to handle transplantation [130]. A composite physiologic index predicts mortality in isolated IPF and may account for disease severity [4], however there are uncertainties regarding its use in CPFE syndrome [17]. In one series that defined CPFE as IPF (with a CT 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 [18]. 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. 22.11).

Pulmonary Hypertension

The main determinant of prognosis in CPFE is represented by PH [7, 16], which develops in up to half of patients with CPFE [7]. PH was present at echocardiography in 47 % of patients in the seminal series of 61 patients [7]. In a cohort of 102 patients diagnosed with CPFE at our center after that publication, PH was present at right heart catheterisation in 48 % of patients with CPFE (Ahmad K and Cottin V, unpublished). When present, PH may cause dilation of the pulmonary arteries at chest radiograph and CT. Newer techniques including magnetic resonance imaging may contribute to the evaluation of PH in CPFE [132], however right heart catheterisation remains the gold standard to diagnose PH.

PH in CPFE is likely due to the synergistic effect of emphysema and fibrosis in reducing the pulmonary capillary bed, with further effect of hypoxia, possible sheer stress, and intrinsic pulmonary vascular abnormalities [133, 134]. In addition, there is accumulating evidence that tobacco smoking may directly contribute to PH [135–137], with obvious relevance in the CPFE syndrome.

Precapillary PH is defined by mean pulmonary artery pressure of 25 mmHg or greater, with pulmonary artery wedge pressure of 15 mmHg or lower. 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 catheterisation [20]. Low cardiac index and high pulmonary vascular resistance are then the main determinants of shorter survival [20]. According to the 2013 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) [138]. In a series of 40 patients with CPFE and PH [20], 68 % had a mean pulmonary artery pressure >35 mmHg [20]; 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; 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 [21], a condition in which PH is frequent.

Lung Cancer

Lung cancer is increasingly recognised in patients with the CPFE syndrome (Fig. 22.12), which is hardly surprising given the increased risk of lung cancer in relation to tobacco-smoking, chronic obstructive pulmonary disease, and IPF [8]. Patients with CPFE may carry an increased risk of lung cancer as compared to those with emphysema alone, and similar to that of individuals with IPF [139]. Emphysema and pulmonary fibrosis were both reported at imaging in 8.9 % of patients with lung cancer in one retrospective study [140].

In a series of 47 patients with lung cancer in the context of CPFE [10], 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 parenchymal 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 [93, 140]. 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 [10, 141, 142].

Among patients with lung cancer, those with CPFE seem to have a worse outcome as compared to patients with either emphysema or fibrosis [140]. Acute exacerbation of fibrosis is a major complication in patients with CPFE, and may occur during treatment for lung cancer, especially following

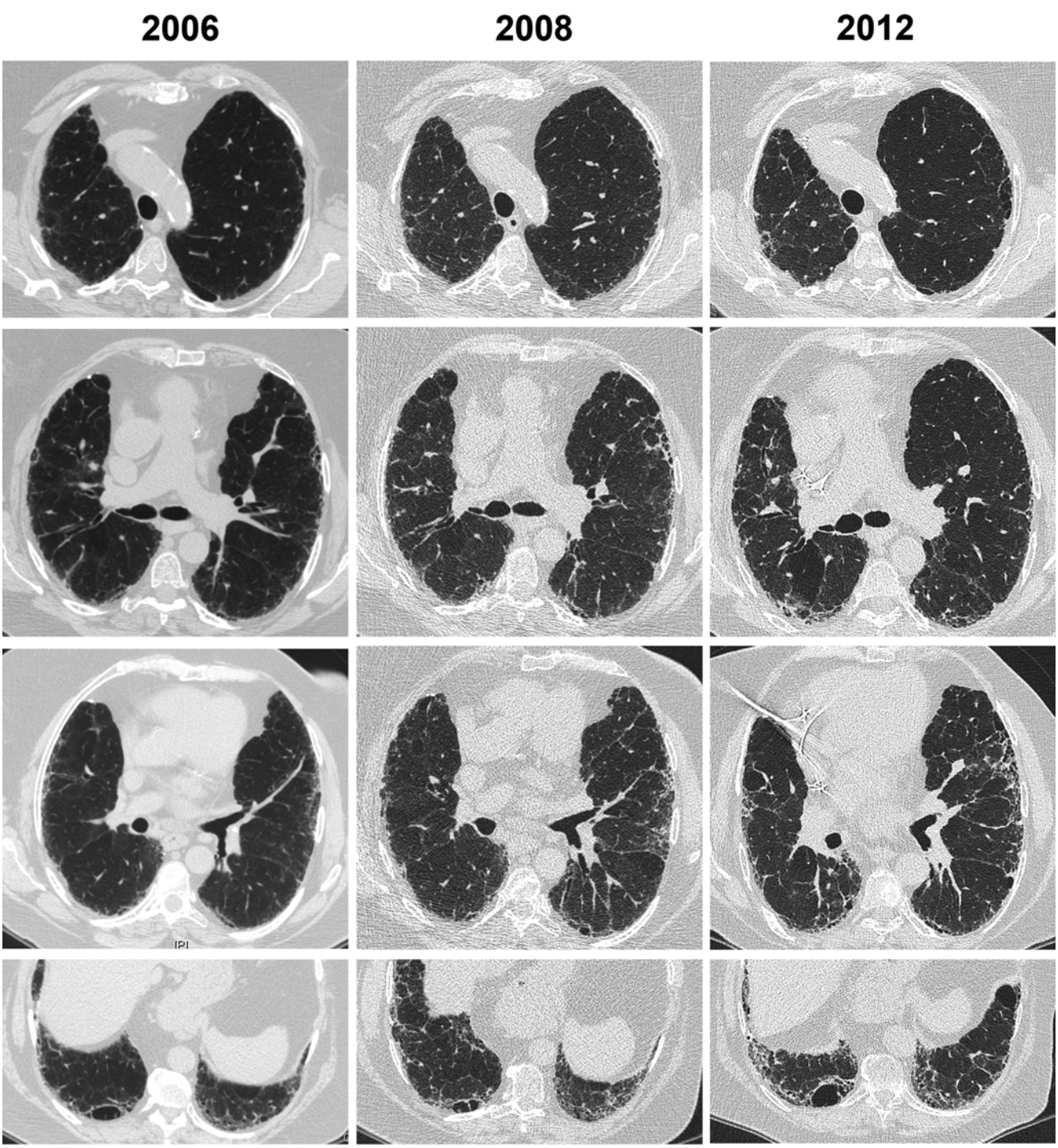

Fig. 22.11 Example of slow progression of disease in a woman with smoking-related CPFE syndrome (chest CT), who quit smoking at diagnosis. Only mild centrilobular emphysema is present in the upper lobes. Subpleural reticular changes predominate, which progress to a pattern of possible usual interstitial pneumonia. A thick-walled large cyst is present in the right lower lobe, which increases in size

radiation therapy [10] or surgery [10, 106, 140, 143]. Acute respiratory distress syndrome may also follow chemotherapy for lung cancer [144]. 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 [10].

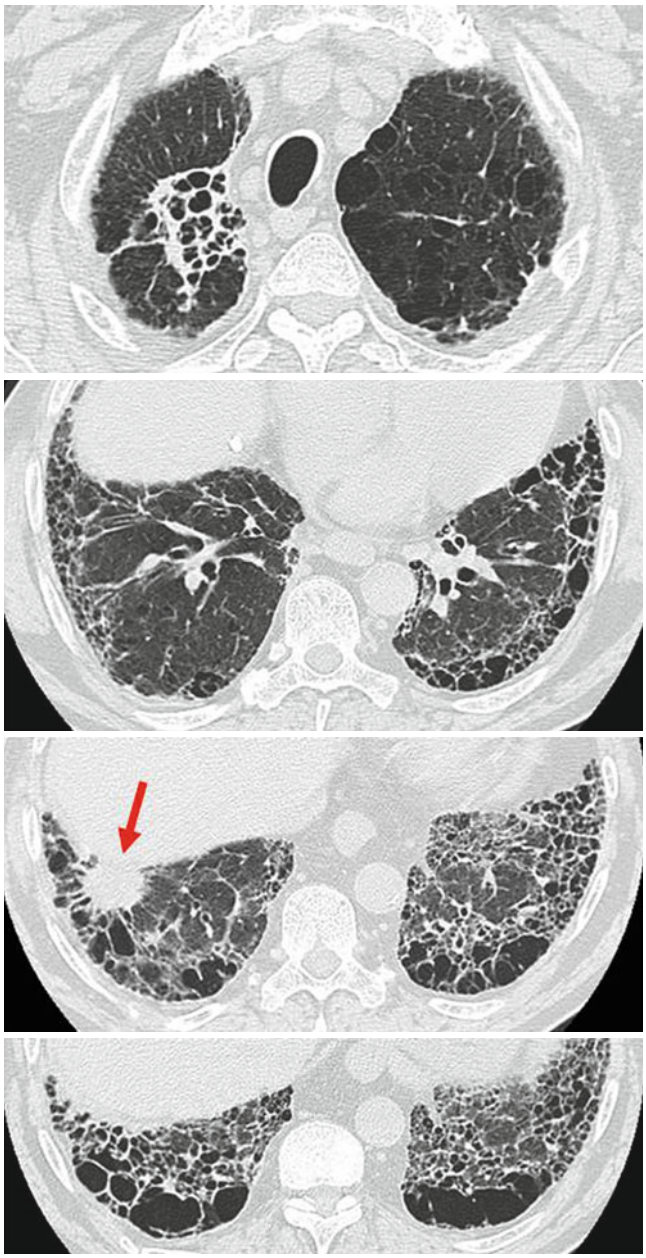

Fig. 22.12 Non-small cell lung cancer (squamous cell carcinoma) in a male patient with smoking-related CPFE syndrome (chest CT). *Upper panel*: centrilobular emphysema in the left upper lobe (and post-infectious bronchiectasis in the right upper lobe); *upper middle panel*: lower zones showing usual interstitial pneumonia pattern with honeycombing; *lower middle panel*: cancer as 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

Acute Exacerbation of Pulmonary Fibrosis

The natural course of disease in CPFE may encompass episodes of acute exacerbation of pulmonary fibrosis [21, 106] similar to IPF [145]. In a series of 93 patients with CPFE, 24 % developed acute exacerbation [106]. 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 [145]. Interestingly, a recent 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 [146], 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 [147]. These observations suggest that patients with the CPFE syndrome may be at particularly high risk of acute exacerbation of pulmonary fibrosis.

Other Comorbidities and Complications

Comorbidities especially related to tobacco-smoking are frequent in CPFE [7]. As in IPF [148] 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 yet 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. According to the most recent international guidelines, there are no data on which to make recommendations for treatment of emphysema in the setting of IPF [117]. Inhaled bronchodilators may be beneficial on dypsnea and cough, and seem to be underutilised [18]. Long-term oxygen therapy is often required, especially when severe PH is present [7, 20]. Patients with severe disease and especially with PH should be referred for lung transplantation, however it is contra-indicated in most patients because of age and comorbidities [7, 18, 20].

Treatment of Pulmonary Fibrosis

Management of pulmonary fibrosis in CPFE generally may follow that of IPF. Two drugs were recently demonstrated efficacious to slow progression of disease in IPF, namely pirfenidone and nintedanib. In patients with IPF and mild to moderate disease severity (e.g. with FVC of 50 % of predicted or greater, and DLco of 35 % of predicted or greater), pirfenidone reduces the progression of disease and decline in FVC by about half, with furthermore improvement in the overall survival at 1 year [149, 150]. In patients with IPF and FVC greater than 50 % of predicted value and DLco comprised between 30 and 79 % of predicted, the triple tyrosine kinase inhibitor nintedanib reduced the annual rate of decline in FVC, consistent with a slowing in disease progression, and increased time to the first adjudicated acute exacerbation of IPF (prespecified sensitivity analysis of pooled data) [151]. As most patients with significant emphysema were excluded from these studies, no 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. Therapeutic trials should be designed specifically to include patients with CPFE, likely using endpoints that do not rely on physiologic surrogates such as FVC [11, 152]. Although recent data have recommended against combination therapy with prednisone, azathioprine, and high-dose N-acetylcysteine in patients with definite IPF, oral corticosteroids and occasionally immunosuppressive therapy may be considered in patients with HRCT patterns more suggestive of NSIP or DIP. Monotherapy using N-acetylcysteine as an anti-oxydant (e.g. 1.8 g per day) has little if any efficacy in IPF [153]. Gastro-esophageal reflux disease when present may enhance progression of pulmonary fibrosis [154] 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 [134] is beyond the scope of this chapter. Available data do not support the use of drug therapies specific for PH in the setting of chronic respiratory diseases [138], however very few clinical studies have been conducted specifically in this context.

Isolated observations [20, 155–157] and data from prospective registries (www.clinicaltrials.gov, NCT01443598) indicate that drugs specific for PH may occasionally improve hemodynamics, but the potential clinical and survival benefit is unknown. Further research is needed to evaluate the potential clinical benefit of PH therapy especially in patients with preserved 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 as defined by mean pulmonary artery pressure of 35 mHg or greater (or 25–34 mmHg along with cardiac index less than 2 L/min/m^2). Treatment with PH drugs may occasionally worsen gas exchange in patients with chronic respiratory disease. Although clinical and hemodynamic improvement was obtained in isolated cases, there is currently no evidence to support the use of PH drug therapy in this setting.

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23 Non-specific, Unclassifiable, and Rare Idiopathic Interstitial Pneumonia: Acute Interstitial Pneumonia, Respiratory Bronchiolitis Interstitial Pneumonia, Desquamative Interstitial Pneumonia, Nonspecific Interstitial Pneumonia

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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	Non-Specific Interstitial Pneumonia
RB	Respiratory Bronchiolitis
RB-ILD	Respiratory Bronchiolitis Interstitial Lung Disease
TPMT	Thiopurine Methyltransferase
UCTD	Undifferentiated Connective Tissue Disease
UIP	Usual Interstitial Pneumonia

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Acute Interstitial Pneumonia (AIP)

Clinical Vignette

A 34 year old woman with a history of hypothyroidism presented 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 1 day prior to presentation. On exam she is mildly tachycardic with a heart rate in the low 90s (her baseline is 60s–70s), but 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 instructions to rest, drink fluids, and call back with any change in symptoms.

Over the next 3 days her cough persisted, and she developed shortness of breath with exertion. She went to the emergency department for further evaluation and was tachycardic with a heart rate in the low 100 s. Her oxygen saturation was 89 % on room air. She had soft, diffuse crackles on exam. A chest radiograph demonstrated hazy opacifications bilaterally, without focal consolidation (Fig. 23.1). A pulmonary embolus protocol CT was negative for pulmonary embolus but showed diffuse patchy ground glass opacifications (GGO) without effusions (Fig. 23.2). She was admitted to the hospital and developed progressive respiratory failure requiring intubation for hypoxic respiratory failure on the second day.

Her labs were notable for a leukocytosis with a white blood cell count of 14,000 and differential showed 82 % neutrophils. Urinalysis showed no

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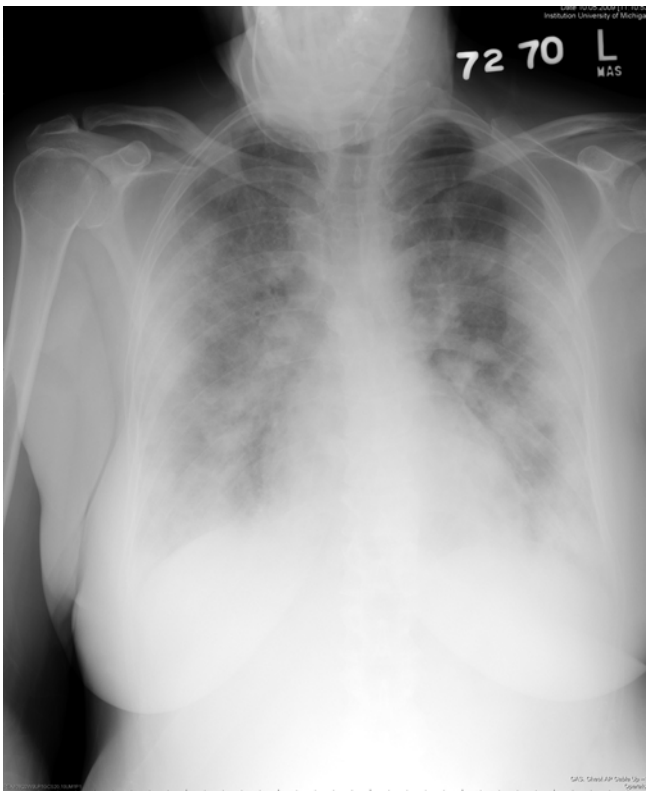

Fig. 23.1 Chest radiograph from a patient with acute interstitial pneumonia demonstrating diffuse bilateral infiltrates without focal consolidation

evidence of infection, and blood cultures were negative. A transthoracic echocardiogram showed no evidence of increased pulmonary arterial or right ventricular pressure, and no left ventricular dysfunction. On her fourth day of hospitalization, given her lack of improvement on broad-spectrum antibiotics, she was started empirically on one gram of methylprednisolone per day. A lung biopsy was performed on her sixth day of hospitalization, and revealed diffuse alveolar damage.

History and Definition

Acute interstitial pneumonia (AIP) – also called Hamman-Rich syndrome – is a rapidly progressive diffuse parenchymal lung disease of unknown etiology resulting in hypoxemic respiratory failure which is often fatal. The presentation – both clinically and radiographically – is virtually identical to Acute Respiratory Distress Syndrome (ARDS) but occurs in the absence of shock or infection [1].

By definition, AIP is idiopathic and thus granulomatous diseases, autoimmune diseases, infections or other exposures that could cause interstitial lung disease (ILD) must be excluded.

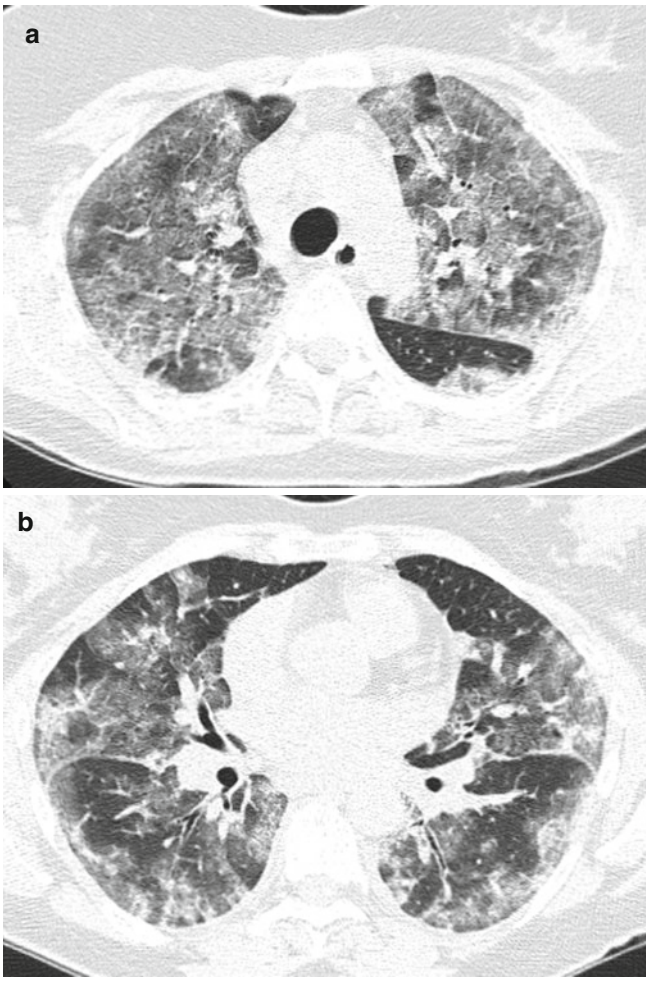

Fig. 23.2 High resolution computed tomography images from the upper (panel **a**) and mid (panel **b**) lung fields demonstrating diffuse bilateral ground glass opacifications without consolidation or effusions

Epidemiology

Acute interstitial pneumonia is a relatively rare but probably underdiagnosed disease. Review of the literature suggests that an individual academic institution may diagnose only a few cases a year, if any [2, 3]. AIP is often a diagnosis of exclusion and requires biopsy confirmation; therefore it is possible that there is a subset of self-limited cases that improve with supportive care and go unrecognized. Conversely, there may be fatal cases that are misclassified as ARDS or pneumonia that never undergo confirmatory biopsy [3].

Age of onset is quite variable, and both pediatric patients as well as the elderly can be affected [4]. No clear risk factors have been convincingly identified in the literature – specifically there is no known link with tobacco exposure – and many of those affected are in good health with no comorbidities.

Presentation

Presenting symptoms vary from patient to patient, but often include cough, dyspnea and occasionally fever. Many patients present with symptoms mistaken for a viral upper respiratory tract infection [5, 6].

Shortness of breath is a hallmark feature and is eventually present in virtually all cases. Given the relatively non-specific historical features, this condition is commonly misdiagnosed early on as pulmonary embolism, infection or congestive heart failure [2].

Physical exam findings are relatively non-specific, including diffuse crackles. Virtually all patients with fulminant AIP are too ill to perform pulmonary function testing, but they would likely reflect diffuse alveolar and bronchiolar damage, showing a restrictive pattern with reduced DLCO [7]. All patients should be examined for joint deformities or skin changes that might suggest the presence of connective tissue disease.

Diagnostic Evaluation

Thorough evaluation for infectious etiologies – particularly viral infections and atypical infections such as pneumocystis pneumonia, legionella, mycoplasma and fungal infections – should be pursued. Cultures of blood and sputum, as well as bronchoalveolar lavage (BAL), are frequently performed. A transthoracic echo to evaluate for left ventricular dysfunction is often obtained. Most patients have a leukocytosis at time of presentation [6].

Bronchoalveolar lavage (BAL) findings are indistinguishable from ARDS and typically include increased total cells, red blood cells, hemosiderin and neutrophils [8]. These findings while supportive are not diagnostic, and the chief utility of a BAL is to exclude other etiologies of respiratory failure and exclude infection. Bronchoalveolar lavage (BAL) can also exclude pulmonary hemorrhage, especially in a patient where a systemic vasculitis or connective tissue disease is suspected.

A thorough medical history should be taken from the patient or family members to clarify whether the patient has received any chemotherapy, has had any previous radiation exposures or whether there is any past history of connective tissue disease. A positive rheumatoid factor in a patient with the appropriate phenotype might be worrisome connective tissue associated-ILD. A positive dsDNA or anti-smith antibody would be consistent with SLE, whereas a negative ANA is helpful in excluding SLE as an underlying etiology. Positive anti-Scl-70 would be concerning for systemic scleroderma. Positive anti-Jo antibodies in conjunction with elevated CPK, Aldolase and ALT would be consistent with an anti-synthetase syndrome which can manifest with rhabdomyositis and ILD. A social history to evaluate for any possible drug or occupational exposures is also warranted.

Radiology

Common findings on high resolution computed tomography (HRCT) in AIP are similar to ARDS, including ground-glass attenuation, 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 predeliction for lower lung fields compared to ARDS [9]. Most patients have involvement that is quite diffuse, involving 45–95 % of lung parenchyma [3]. There is some evidence that the presence of traction bronchiectasis may reflect fibrosis and portend a worse outcome [10].

Histopathology

Establishing a histopathologic diagnosis is requisite for diagnosing AIP, and furthermore can be helpful in excluding other more treatable disease states such as sarcoid or infection. Open lung biopsy will best demonstrate the architectural and histopathologic changes. 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 needed pathologic characteristics [1, 7]. Many diagnoses are made on autopsy [10].

Although helpful from an academic standpoint, there is very little in the way of therapeutic options available for AIP which means obtaining a tissue diagnosis may not provide much benefit depending on the clinical scenario. If infection has already been excluded with BAL, many practitioners would trial empiric steroids rather than pursuing a biopsy-confirmed diagnosis. One can imagine specific scenarios where the risks of a biopsy would be too high to the patient to warrant the procedure, whether secondary to clinical instability or bleeding risk. Alternatively, there may be instances in which a definitive diagnosis might alter goals of care. This highlights the importance of determining whether to pursue histopathologic diagnosis on a case-by-case basis.

The histopathologic hallmark of AIP is diffuse alveolar damage. Alveoli containing inflammatory cells – lymphocytes, plasma cells and macrophages with occasional neutrophils – are often seen. The remnants of hyaline membranes within alveoli are frequently observed. Other key features on biopsy are interstitial fibrosis and edema, as well as the presence of type II pneumocyte hyperplasia [5] (Fig. 23.3).

A key feature that distinguishes AIP from more chronic processes is the presence of extensive fibroblast proliferation

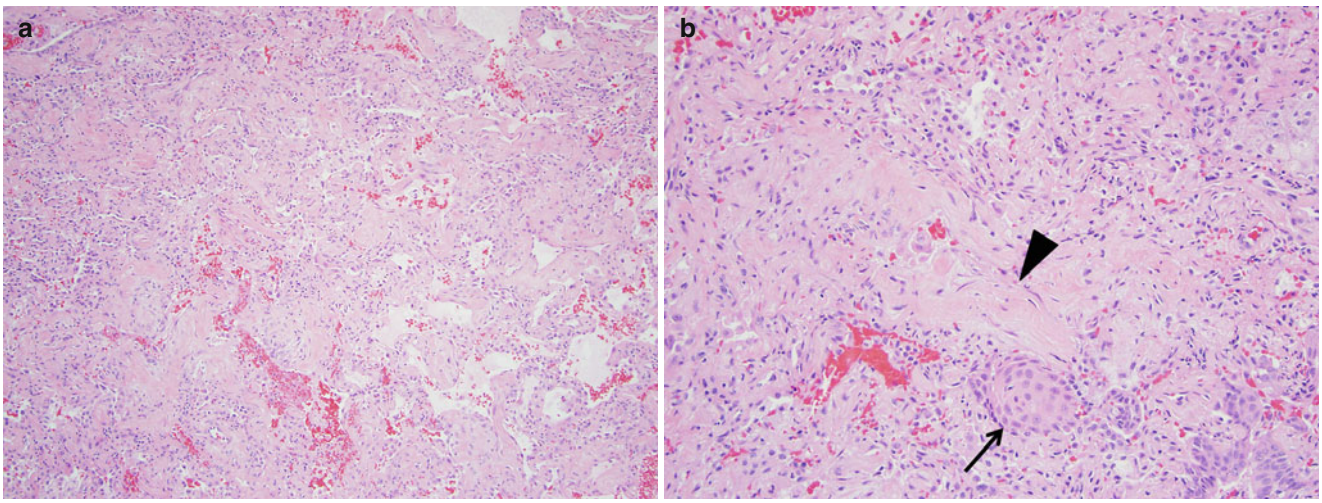

Fig. 23.3 At low power (panel **a**), acute interstitial pneumonia is characterized by diffuse interstitial thickening with associated alveolar septal collapse. At higher magnification (panel **b**), subepithelial proliferations of fibroblasts and myofibroblasts in a myxoid collagen background are common (*arrowhead*) and residual hyaline membranes are usually not prominent. Squamous metaplasia (*arrow*), although a nonspecific finding, is common in acute interstitial pneumonia

and relative absence or paucity of collagen deposition. Another helpful differentiating characteristic is the relative uniformity of disease from field to field, as compared to a chronic interstitial pneumonia, which reflects multiple insults with varying degrees of inflammation and fibrosis [5]. Architectural distortion, when observed, is generally associated with a poor prognosis.

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 the point of requiring admission to an intensive care unit [2]. Most patients become rapidly ventilator dependent secondary to refractory hypoxemia. The mortality rate is greater than 50 %, and average time to death averages approximately 2 weeks [2, 5, 7]. The minority of patients who survive AIP generally do well in the absence of other comorbidities. While there have been some reports of recurrent AIP and many patients go on to develop ILD, some patients do not have any clinically significant pulmonary sequellae [3, 6].

Pathophysiology

Similar to ARDS, AIP is characterized by diffuse alveolar damage comprised of an exudative phase, early proliferative phase and a late proliferative phase, which in some cases evolves to extensive fibrosis [11].

In the exudative phase, acute alveolar epithelial damage results in the release of inflammatory mediators and recruitment of macrophages, lymphocytes, plasma cells and neutrophils. This overwhelming immune response results in interstitial edema and further epithelial injury. The initial robust immune response is followed by an organizing phase characterized by fibroblast proliferation and thickening of the alveolar septae [6]. The rapidity of progression varies from patient to patient, but typically the pattern of injury is uniform, reflecting a simultaneous insult rather than multiple insults at different points in time.

Treatment

Initial treatment is both empiric and supportive. 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, usually with BAL.

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 [3, 7, 12]. 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. 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 [3].

Respiratory Bronchiolitis Interstitial Lung Disease (RB-ILD)/Desquamative Interstitial Pneumonia (DIP)

Clinical Vignette

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. Additionally, 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 on autopsy series of young cigarette smokers who died of non-pulmonary causes. The histopathologic features are characterized by clusters of brown pigmented macrophages in the first-order and second- order respiratory bronchioles [13]. Clinically, RB is associated with asymptomatic or a minimally symptomatic disease state characterized by mild cough and/or dyspnea [13–15]. In rare cases, RB may present with significant pulmonary symptoms, abnormal imaging and pulmonary function testing. In this scenario it is described as RB associated interstitial lung disease (RB-ILD) [1].

Epidemiology

RB-ILD lies on a spectrum of smoking-related lung diseases that ranges from minimally symptomatic RB to very severe but pathologically similar desquamative intertstitial pneumonia (DIP). RB-ILD was first introduced by Myers et al as pathologic explanation for a clinically described chronic ILD where RB was the only pathologic diagnosis seen on biopsy [16, 17]. RB-ILD has since been further characterized as a distinct clinical entity, albeit very rare.

Presentation

The majority of patients present with nonspecific respiratory complaints including gradual onset of dyspnea and new or changing cough. 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 [15]. Rarely, do patients have any clubbing [1, 14, 15, 17]. RB-ILD is seen in patients in the fourth and fifth decades of life and the patients are usually heavy smokers (>30 pack years) with a 2:1 male predominance [1, 14, 17].

Diagnostic Evaluation

The pulmonary function testing (PFT) pattern most often seen in RB-ILD is obstructive, however, both restrictive and a mixed patterns are seen frequently as well. 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 [16]. However, 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, 18]. Approximately, 10 % of patients have normal lung function at diagnosis [19].

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, 14, 15]. HRCT is more clinically useful and frequently shows nonspecific changes such as centrilobular nodularity and patchy GGO

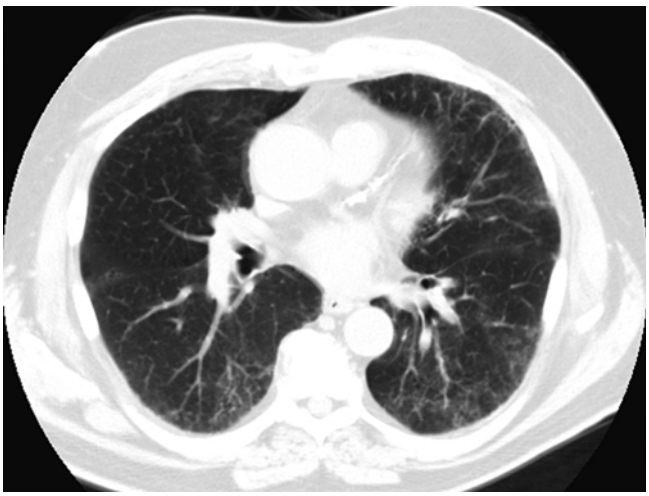

Fig. 23.4 High resolution computed tomography images from a patient with respiratory bronchiolitis interstitial lung disease demonstrating areas of faint, patchy ground glass opacification and reticular thickening

with septal thickening (Fig. 23.4). The radiographic differential includes hypersensitivity pneumonitis and non-specific interstitial pneumonia (NSIP) [20]. Since all of these patients are smokers or former smokers, concomitant emphysema is common as well.

Histopathology

The next step in the work up of RB-ILD usually includes a bronchoscopy, as is the case with many ILDs. In the case of suspected RB-ILD bronchoscopy is not typically helpful. 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, 18]. 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. Histopathologically RB-ILD differs from RB by demonstrating fibrous scarring that extends into the surrounding alveolar wall in addition to the aforementioned clusters of pigmented macrophages [16, 17]. These clusters are more frequently found near the bronchioles as compared to the rest of the lung parenchyma. Additionally, these clusters are more prominent than those seen in healthy cigarette smokers [15]. RB-ILD lacks features of usual interstitial pneumonia (UIP) such as honeycombing and fibroblastic foci. Concominant emphysema may be seen as well in RB and RB-ILD, owing to the strong association with smoking [16] (Fig. 23.5).

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 it was a benign disease process however, more recent studies suggest that RB-ILD has a more sinister course [18, 21–23]. 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 [18]. There have been no deaths reported due to RB-ILD.

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 [15, 18]. In some cases a trial of corticosteroids is used. Once again, results are mixed but recent studies suggest that there is no consistent improvement in symptoms or pulmonary function with corticosteroid treatment and therefore is not routinely recommended [18]. Empiric dosing of prednisone 0.5 mg/kg/day has been tried. The overall course is short (~4–6 weeks) and is usually reserved for patient with a documented decline in lung function despite abstinence from smoking [24]. It is unclear whether or not any intervention alters the natural history of the disease.

Desquamative Interstitial Pneumonia (DIP)

History and Definition

As mentioned above, DIP is another smoking related ILD thought to be on the severe end of the spectrum with 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. These include extensive desquamation and proliferation of large alveolar cells within the alveolar space which contain PAS positive brown colored granules, accumulation of lymphoid follicles in the periphery of the lung, slight thickening

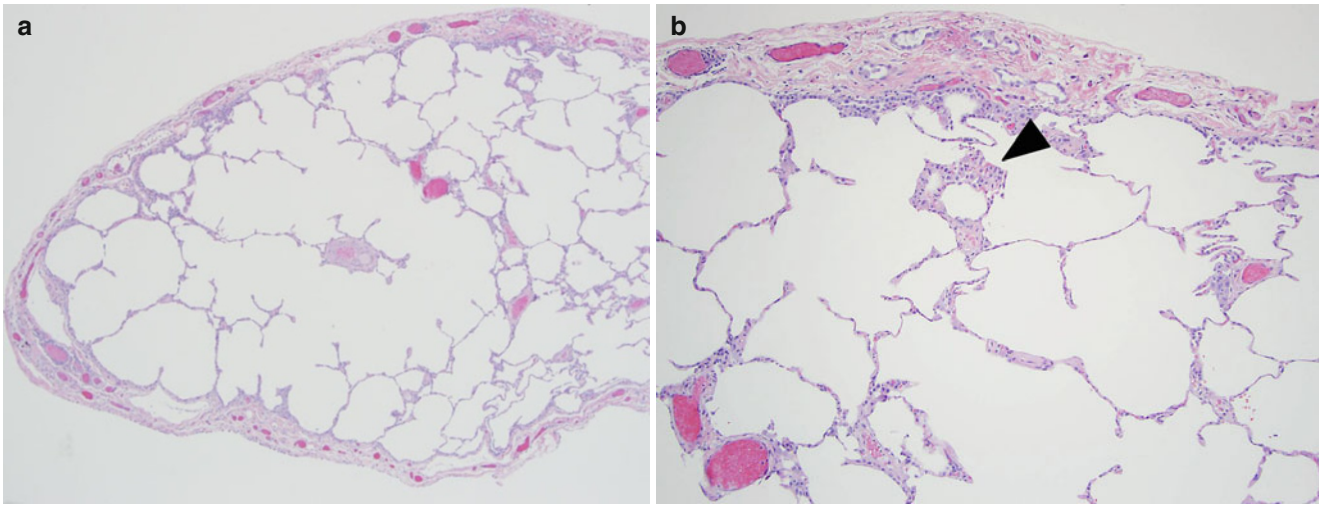

Fig. 23.5 The main histologic finding of respiratory bronchiolitis interstitial lung disease is similar to that of desquamative interstitial pneumonia; namely increased numbers of intraalveolar macrophages (panel **a**). This process is limited to the small bronchioles and peribronchiolar airspaces (*arrowhead* 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

of the alveoli without any evidence of necrosis, hyaline membranes or fibrinous exudates and uniform lesions throughout the lungs [25]. DIP was further expanded upon in 1978 by differentiating it from UIP [26]. In 1987, Myers et al. were the first to consider that RB-ILD may evolve into DIP [17]. The true relationship between DIP and RB-ILD is not well understood due to the rarity of both diseases. Since RB, RB-ILD and DIP are generally considered on the same spectrum of disease it is important to be able to differentiate between them. This distinction is especially important because each process has a different natural history. Specifically, there is increased morbidity and mortality associated with DIP as compared to RB and RB-ILD [27].

Epidemiology

Approximately 90 % of patients with DIP are smokers or former smokers although it can be seen with systemic disorders, infections and environmental triggers [22, 23, 26]. 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 150 reported cases in the literature [28]. 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 or other diagnoses [24].

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, 22]. On exam, most patients have inspiratory crackles and clubbing is common as well [1, 22, 23, 26]. 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 exam, 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 [22, 23]. Pulmonary physiology may show normal lung volumes or varying amounts of restriction. This is consistent with the major pathology

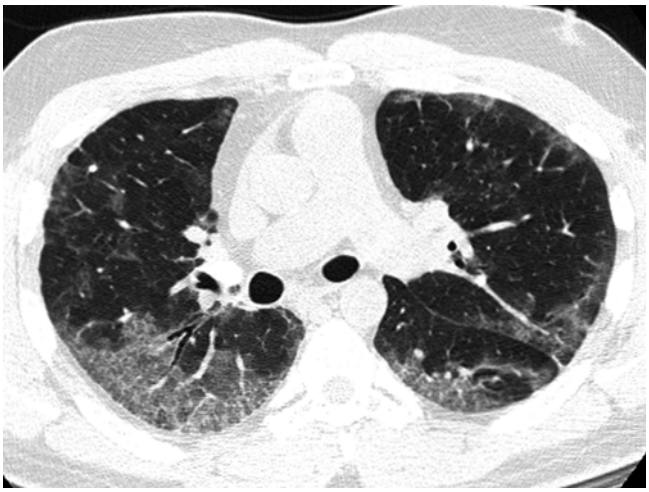

Fig. 23.6 High resolution computed tomography images from a patient with desquamative interstitial pneumonia showing patchy ground glass opacification in a lower and peripheral lung zone distribution

being a fibrotic process. The major and most consistent PFT abnormality is impairment in gas exchange signified by a low DL_{CO} [23, 26].

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, 22, 26]. HRCT typically shows patchy GGO with a lower and peripheral lung zone predominance as well (Fig. 23.6). 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, 14, 20, 22]. As these patients are 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 jiroveci pneumonia [1, 14].

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. All of these BAL findings are nonspecific.

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 [14, 22, 23, 28]. 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 [21, 23].

Pathologically, these distinctions, as discussed above, involve the amount of macrophage clusters and the presence of fibrous scarring that is seen in RB-ILD [16, 17]. 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, 14, 27] (Fig. 23.7).

Clinical Course

The natural history of untreated disease can range from mild to quite severe, incurring a mortality of 6–30 %. Additionally, acute exacerbations of DIP have been reported, leading to increased morbidity and mortality [22, 23, 27]. Lastly, DIP is generally considered a more severe disease with higher morbidity and mortality than RB-ILD.

Treatment

The course of DIP without treatment is variable and ranges from mild disease to severe respiratory limitations. Spontaneous remissions and acute exacerbations leading to fulminant respiratory failure have been reported as well [26, 27, 29]. There is an associated 5-year mortality of approximately 5 % and 10-year mortality of approximately 30 % [26]. If left untreated two-thirds of patients will have clinical worsening [26].

Treatment consists primarily of smoking cessation although few studies have shown clear clinical benefit [22, 26]. In a summary of studies dedicated to DIP a response rate of 71.2 % was found when systemic corticosteroids were used. The recommended dose of prednisone is around

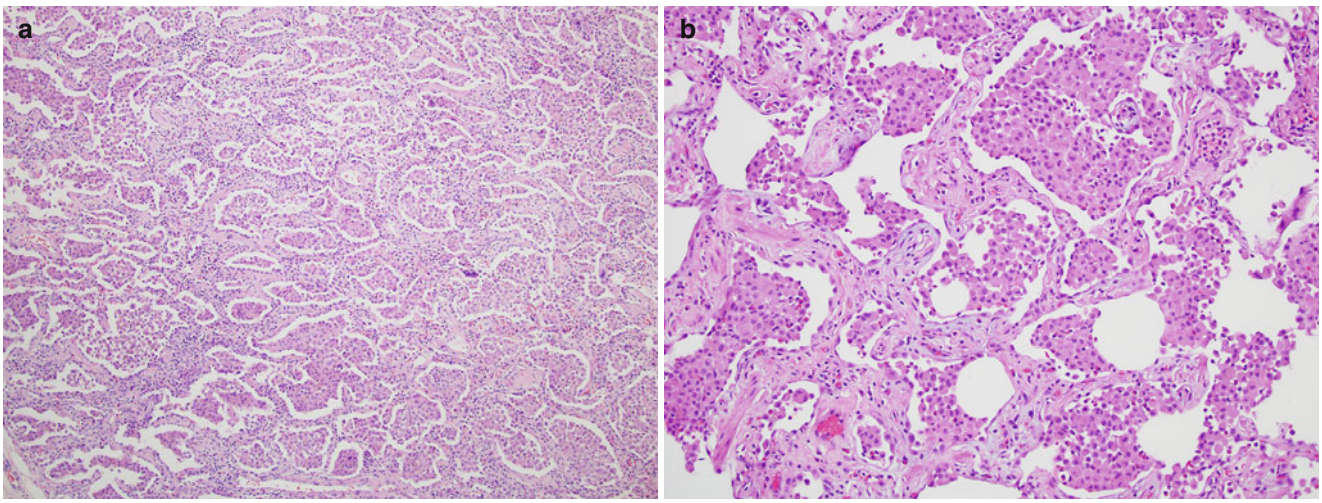

Fig. 23.7 At low power (panel **a**), the main histologic finding of desquamitive interstitial pneumonia is increased numbers of intraalveolar macrophages. At higher magnification (panel **b**), the macrophages contain the coarsely granular, golden brown smoker's pigment. Mild alveolar septal fibrosis is also a common finding

0.5 mg/kg daily. The duration of steroids varies but is usually tapered over 3–6 months [24]. Additional reports mention further immunosuppression with azathioprine and cyclophosphamide in refractory cases but the response rates to these therapies was not discussed [28]. With treatment, reversal of the GGO seen on CT may improve or disappear [1, 14]. Additionally patients who are treated may fully recover lung function [26]. In extreme cases, those patients who continue to progress despite treatment may be referred for lung transplantation.

Non-specific Interstitial Pneumonia (NSIP)

Clinical Vignette

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 was noted be 92 % on room air. Cardiac exam was normal. Posterior chest auscultation revealed 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 was normal.

Pulmonary function testing performed on the visit showed a mild restrictive ventilatory pattern with mildly impaired gas exchange. Chest x-ray was normal.

Laboratory work drawn in the office showed normal cell counts, and a normal comprehensive metabolic panel. Antinuclear antibody (ANA) titer was positive to a dilution of 1:160, and rheumatoid factor was negative. Anti-Ro/SSA and anti-la/SSB antibodies were also noted to be positive. Computed-tomography images demonstrated diffuse intralobular septal thickening with a significant degree of GGO. The subpleural region was relatively spared throughout the chest. A surgical lung biopsy was planned for the patient given the findings, and her progressive functional decline. The final pathology report demonstrated diffuse fibrosis and inflammation that was temporally homogeneous suggestive of a pattern of NSIP.

History and Definition

Non-specific 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 [30]. This definition has been redefined over time, given concern that it was a "wastebasket" diagnosis [31]. It is well known that the histologic pattern of NSIP can be seen in

association with other disease states such as hypersensitivity pneumonitis, acquired immunodeficiency syndrome [AIDS], connective tissue diseases, and drug induced disease. 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 [32]. 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 [33].

Epidemiology

The incidence and prevalence of idiopathic NSIP are unknown. Since Katzenstein and Fiorelli's description of NSIP in 1994 [30], several cases that were previously classified as IPF were reclassified as NSIP in 11–43 % of cases [34]. Given the known prevalence of IPF, the extrapolated prevalence of idiopathic NSIP could range from 1 to 9/100,000 [34]. 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 most common patient with NSIP is a middle-aged adult presenting with cough and dyspnea that had developed over weeks to months prior to diagnosis [30, 31]. Two-thirds of the patients are women, and unlike patients with IPF, 70 % are never smokers [31]. Patients may have nonspecific symptoms such as fever [31] and serologic abnormalities (antinuclear antibodies and rheumatoid factor) are common [35]. Many patients with NSIP meet the case definition of undifferentiated connective tissue disease, suggesting an autoimmune process [35]. 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 [35].

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 [36]. Pulmonary function testing demonstrates a restrictive ventilator 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. 23.8). Though the lower lobes are involved, there is not as much of a clearly defined apical-basal gradient as seen in UIP [30, 31].

The most frequently seen HRCT findings are increased reticular markings, traction bronchiectasis, lobar volume loss, and GGO [31, 37] (Fig. 23.9). Other findings in late stage NSIP are subpleural cysts, or honeycombing, which are smaller and less extensive compared to those found in UIP [37]. If honeycombing is the predominant finding, UIP should be favored as the diagnosis [37–39]. Additionally,

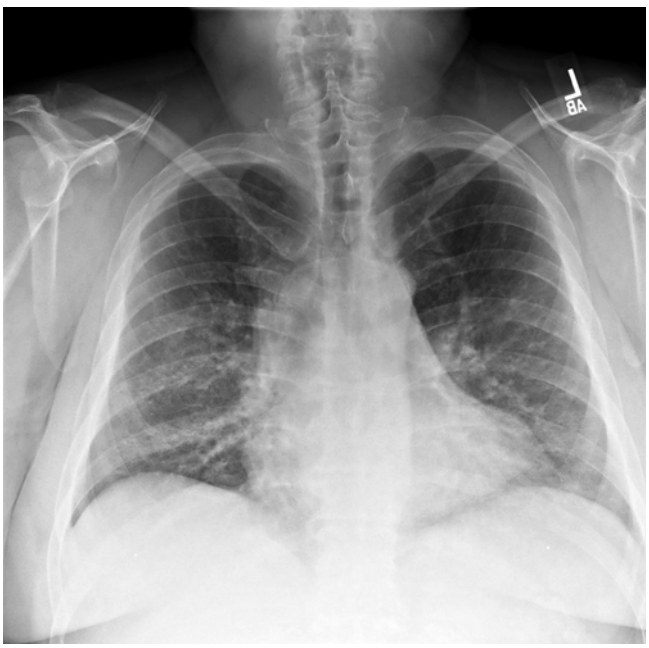

Fig. 23.8 Chest radiograph from a patient with nonspecific interstitial pneumonia showing bilateral interstitial infiltrates

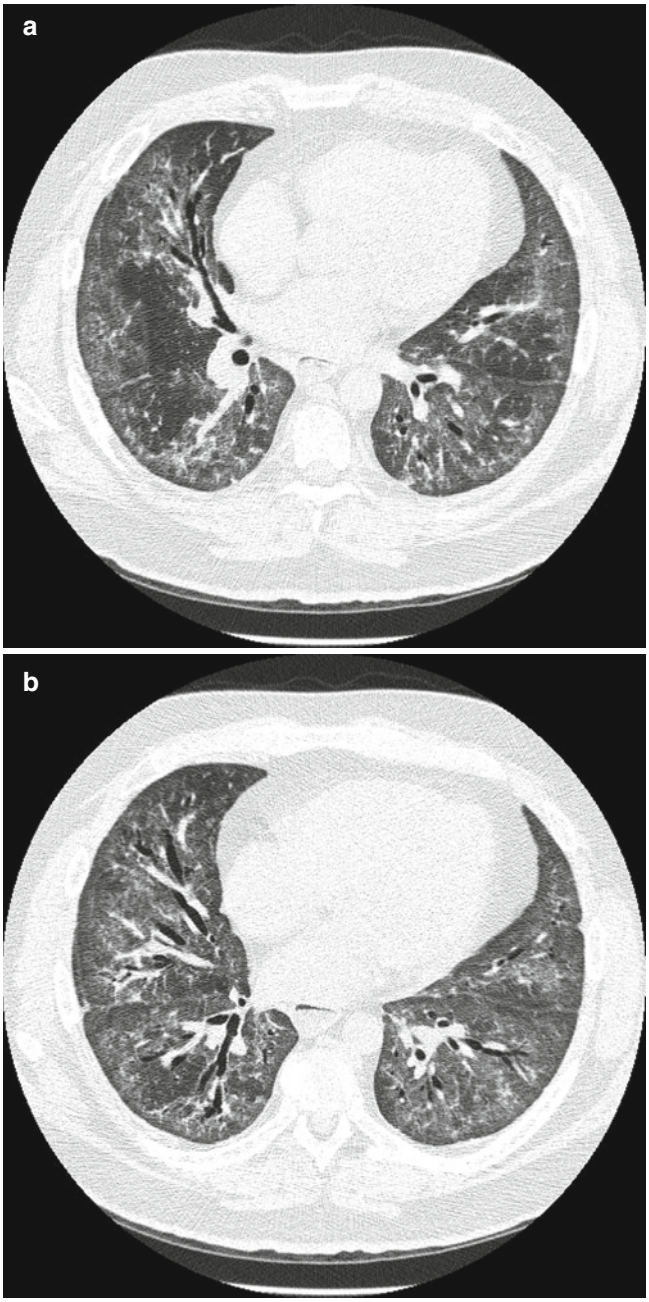

Fig. 23.9 High resolution computed tomography from the mid (panel **a**) and lower (panel **b**) lung fields of patient with nonspecific interstitial pneumonia. The images demonstrate patchy areas of ground glass opacification, reticular thickening and traction bronchiectasis. Some subpleural sparing of disease can be appreciated. Honeycombing is absent

areas of GGO do not progress to honeycombing on serial HRCTs in NSIP, whereas this progression can be seen in UIP [32].

Despite typical HRCT findings, the ability to make a definitive diagnosis of NSIP via HRCT is limited [40]. Unlike UIP, the accuracy of HRCT for diagnosing NSIP can range from 66 to 68 % [38, 41]. Given the significant differences 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 [35].

Histopathology

Bronchoscopy, while useful to rule out infection or other types of interstitial lung diseases such as sarcoid, cannot make a specific diagnosis of NSIP. When evaluated, bronchoalveolar 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) [42, 43].

A surgical lung biopsy is required to make a definitive diagnosis of NSIP. 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, 44]. Temporal homogeneity is the major feature which distinguishes NSIP from UIP, the histologic pattern for idiopathic pulmonary fibrosis. 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 finding (fibrotic NSIP). This third group is differentiated from UIP by the absence of fibroblast foci and the presence of temporal homogeneity [30]. 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 [45, 46]. Further complicating this process, both NSIP and UIP patterns can be found in the same individual when biopsies are taken from multiple locations in 13–26 % of patients [47, 48]. Those with discordant biopsy results have a prognosis similar to UIP, and should be considered to have UIP in all lobes (Fig. 23.10).

Clinical Course

Patients with NSIP tend to have a better prognosis and response to treatment compared to those with UIP/IPF [42, 44, 49]. This difference persists after adjusting for age, gender, smoking history, and physiologic variables. Survival is the greatest 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.

Treatment

Glucocorticoids are the mainstay of therapy for patients with NSIP. The optimal dose and duration of glucocorticoid

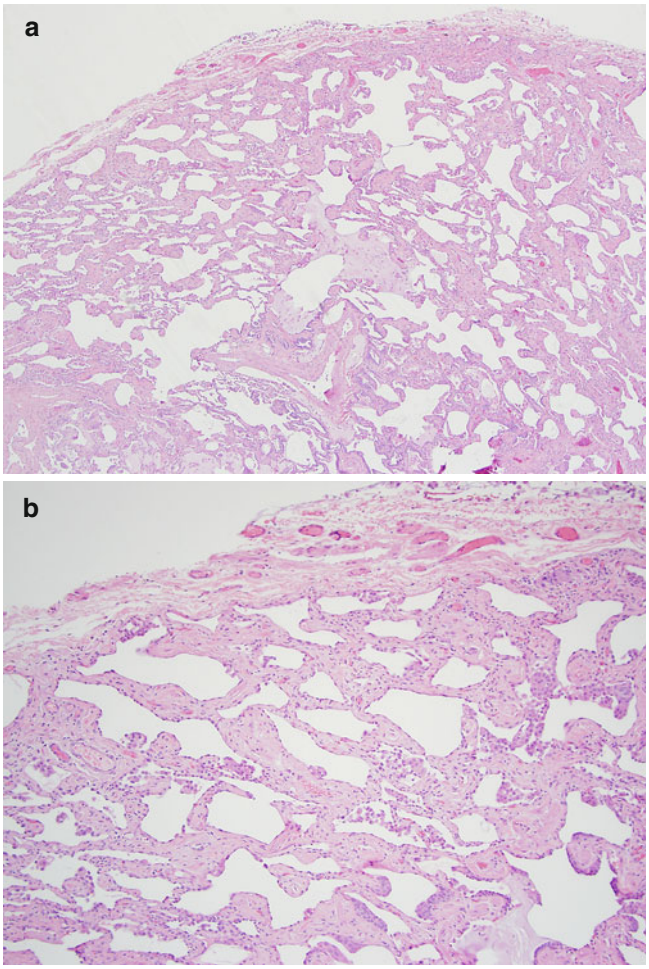

Fig. 23.10 At low power (panel **a**), fibrosing nonspecific interstitial pneumonia demonstrates prominent, uniform septal thickening by mature collagen. At higher power (panel **b**), the septal thickening is due mainly to thick collagen with minimal inflammation

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 [30, 36, 42, 44, 50].

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 [51]; consideration of a longer prednisone course or steroid-sparing agents such as cyclophosphamide, azathioprine or mycophenolate is appropriate in this cases. Combination therapy has also been shown by Kondoh et al. [52] 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 1,000 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. After pulse therapy, 33 % of patients with NSIP had improved VC % pred versus 15 % with IPF. After 1 year of combination therapy, 66 % of patients with NSIP had improved versus 15 % of the IPF group.

Cyclophosphamide has also been used as a sole agent with either known or suspected NSIP [50]. 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. In patients with severe, progressive NSIP or disease that is refractory to immunosuppressive therapy, lung transplantation can be considered [53]. 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 a multidisciplinary clinical, radiographic and pathologic review of data there are some cases that remain unclassifiable. This situation typically occurs when either a key piece of data are missing or the data available are internally inconsistent. 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 or radiographic information
2. Inadequate or nondiagnostic biopsy (due to sampling error or size)
3. Major discrepancy between the clinical, radiographic, and pathologic findings such as varied biopsy patterns in different areas of the lung or discrepancy between radiographic and pathologic patterns of disease [1].

When these situations arise the recommendation is to decide on treatment based on the most probable diagnosis. A recent retrospective series suggested that this situation may occur in approximately 10 % of cases [54]. In this series the main reasons for not obtaining a final diagnosis related to either not obtaining or an inadequate lung biopsy (77 %) or conflicting clinical, radiographic, and pathologic

data (18 %) [54]. Patients with unclassifiable disease had a better prognosis compared to IPF (HR 1.54, p = 0.12) and a similar survival to other non-IPF diseases (HR 1.54, p = 0.12) [54].

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Organizing Pneumonias

24

Romain Lazor

Abbreviations

AFOP	Acute fibrinous organizing pneumonia
BAL	Bronchoalveolar lavage
BO	Bronchiolitis obliterans
BOOP	Bronchiolitis obliterans organizing pneumonia
COP	Cryptogenic organizing pneumonia
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DAD	Diffuse alveolar damage
DNA	Desoxyribonucleic acid
GPA	Granulomatosis with polyangiitis
NSIP	Nonspecific interstitial pneumonia
NYHA	New York Heart Association
OP	Organizing pneumonia
SOP	Secondary organizing pneumonia
TBB	Transbronchial biopsy

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 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 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 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].

Epidemiology

OP represents 2–10 % of all interstitial lung diseases [5–7]. In the only epidemiological study available so far, 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

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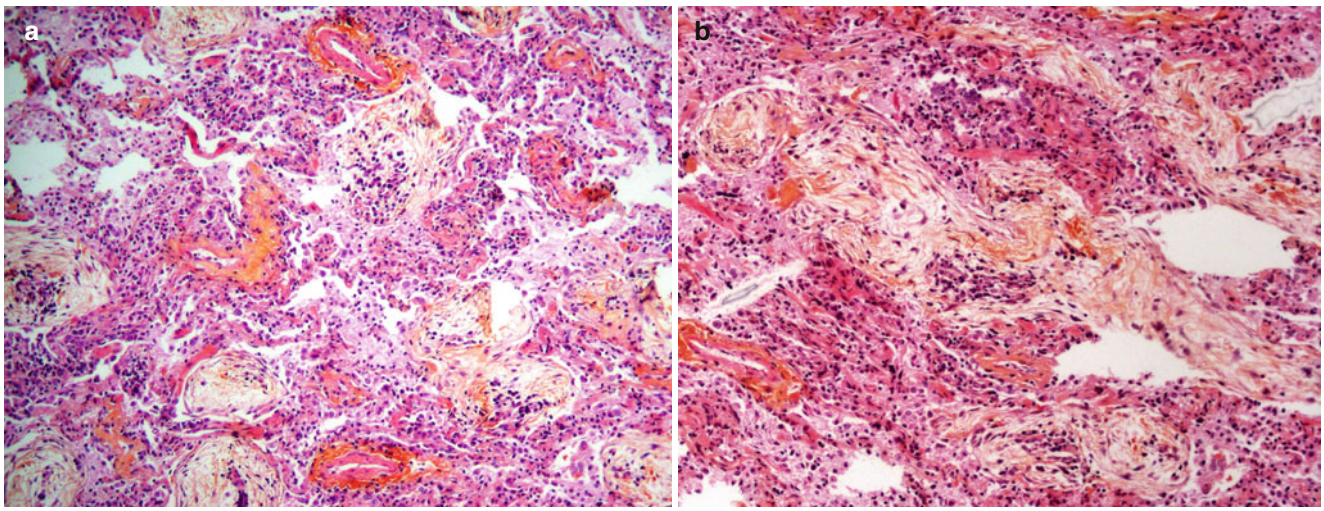

Fig. 24.1 (**a**, **b**) Histopathological pattern of organizing pneumonia at surgical lung biopsy: buds of granulation tissue containing myofibroblasts and inflammatory cells embedded in a loose connective matrix, and filling the alveolar spaces without disruption of the parenchymal architecture. Mild inflammatory infiltrates of the alveolar interstitium

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. 24.1) [2, 11–14].

Intraalveolar fibrosis resulting from organization of inflammatory exsudates in OP is characterized by dramatic reversibility with corticosteroids, in sharp contrast with fibrosis in the other fibrosing idiopathic interstitial pneumonias, especially usual interstitial pneumonia (UIP), which is irreversible. The mechanisms governing the disappearance of myofibroblasts and fibroblasts from alveolar spaces in OP (spontaneously or with corticosteroids) are poorly understood. Apoptosis may play a role, as apoptotic activity is increased in the newly formed connective tissue in OP [15]. Intraalveolar buds in OP are also characterized by prominent capillarization resembling granulation tissue in cutaneous wound healing [16]. Vascular endothelial growth factor and basic fibroblast growth factor are widely expressed in intraalveolar buds, and angiogenesis mediated by these growth factors could contribute to the reversal of buds in OP [17].

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 intraalveolar 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.

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, 18–23].

Disease onset is usually subacute with flu-like symptoms, dry cough, mild dyspnea, fatigue, fever, and weight loss [2, 14, 20, 24]. Productive cough, chest pain, night sweats, arthralgias and myalgias, are less frequent features. Hemoptysis is rare in most large series [23, 25–27], although it has been reported in up to 50 % of cases in one study [28]. Finger clubbing is absent. At chest auscultation, sparse inspiratory crackles are usually heard over the affected areas [26, 27]. Wheezing is uncommon in OP. The frequency of clinical symptoms and signs in a large recent series of OP is summarized in Table 24.1 [27]. No significant difference was found between the clinical presentations of COP and SOP in this series, except for more common crackles in the latter [27]. On rare occasions, OP is incidentally discovered at chest X-ray in an asymptomatic patient [22, 23, 27].

At pulmonary function testing, OP is characterized by mild to moderate restrictive ventilatory defect. Airflow obstruction is found in only a minority of patients, usually smokers [2], and probably reflects preexisting 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, 14, 18, 19]. Severe hypoxemia is rare and may result from right-to-left blood shunting through densely consolidated lung parenchyma [29].

Blood cell count usually discloses moderate leucocytosis and neutrophilia [22, 26, 27]. C-reactive protein level and erythrocyte sedimentation rate are usually increased [14, 26, 27, 30]. Bronchoalveolar lavage (BAL) typically shows a mixed pattern alveolitis [14, 20, 21, 23, 24, 31], 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 [23]. The lymphocyte CD4/CD8 ratio is usually decreased [14, 21, 23, 24, 31], but it has no specific diagnostic value for OP and is therefore not useful in the diagnostic process. Predominance of eosinophils over lymphocytes is uncommon [31] and suggests the diagnosis of eosinophilic pneumonia rather than OP (cases with overlapping features of eosinophilic pneumonia and OP have occasionally been reported).

Table 24.1 Frequency of symptoms and signs in organizing pneumonia

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 %

Adapted from Ref. [27]

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 [22, 23, 26, 32]. It is characterized by multiple bilateral alveolar opacities predominating in the subpleural regions and the lower lung zones, often containing an air bronchogram (Fig. 24.2) [14, 18, 19, 32–34]. A chest computed tomography (CT) 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 [23, 31], either before treatment or when a relapse occurs (Fig. 24.3). This phenomenon called

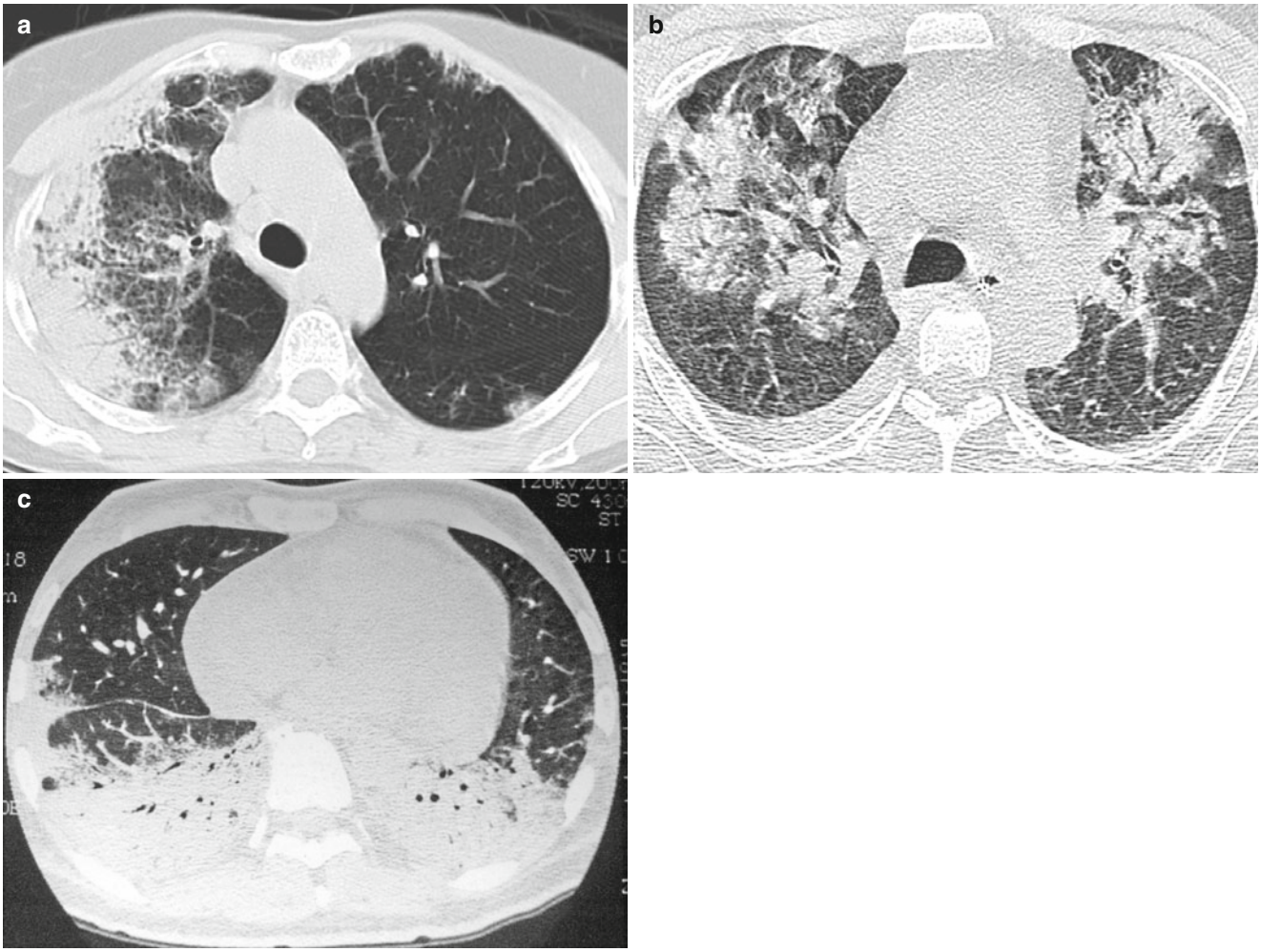

Fig. 24.2 (**a**–**c**) Chest CT scan in the classical multifocal form of organizing pneumonia in three patients: multiple bilateral alveolar opacities with an air bronchogram, mainly located in the subpleural areas and the lung bases

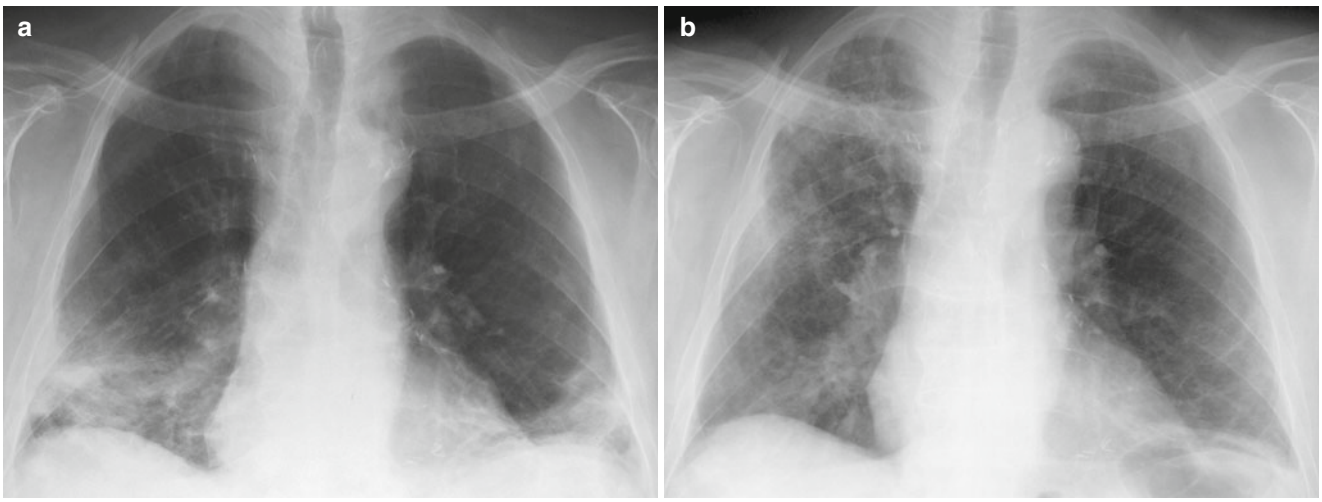

Fig. 24.3 Migratory opacities in organizing pneumonia. (**a**) Bilateral basal subpleural consolidations. (**b**) Three weeks later, spontaneous healing of right basal consolidation and partial regression of left basal consolidation, but appearance of new ground-glass opacities in the middle and upper fields of the right lung (reproduced with permission of Elsevier from Rev Pneumol Clin 2005;61:193-202)

"migratory opacities" provides another important diagnostic clue for OP, as the differential diagnosis is relatively narrow (Table 24.2). Positron emission tomography has shown a significant fluorodeoxyglucose uptake in OP presenting with parenchymal consolidation [35], but this procedure is not part of the routine assessment of OP. Pleural effusion has usually been reported as uncommon in OP [19, 23], although a small effusion has been found in up to 35 % of cases in one series [28]. A moderate enlargement of mediastinal lymph nodes may be found in about 14 % of cases [36].

Isolated Nodular Form

This form has been termed "localized", "solitary", "nodular", or "focal" OP, and represents 5–20 % of cases [14, 22, 26]. It appears as a solitary nodule or mass with smooth or irregular margins [14, 37–41] (Fig. 24.4a). In around half of patients, the lesion is found incidentally [39–42].

In pooled data from five series of nodular OP totalizing 105 cases [39–43], 69 % were men (range across series 56–100 %) and 74 % were smokers or ex-smokers (range 57–72 %, n = 87). Only 47 % were symptomatic (range 17–77 %). A history of recent infection was found in 29 % (range 12–57 %). The upper lobes were affected in 45 % of cases (range 29–58 %, n = 47). The mean size of the nodular opacity was 21 mm (range 6–68 mm). Irregular, lobulated or spiculated margins were present in 72 % (range 54–94 %). An air bronchogram was found in 18 % of cases (n = 47). Satellite nodules were found in 40 % (range 29–56 %, n = 65) and mediastinal lymphadenopathy in 7 % (range 0–19 %, n = 73).

Isolated nodular OP presents with contrast enhancement on CT and positive tracer uptake on positron emission tomography [40, 41], 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 1,612 thoracic surgical procedures performed in a 3-year period at one institution [40]. In 105 patients with nodular OP from five series, preoperative transthoracic or transbronchial biopsy was performed in only 23 % 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 [40, 41]. Of note, in all of 17 non-operated cases, a spontaneous improvement of the opacity was observed [39, 43]. 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.

Table 24.2 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 (Churg-Strauss)
Allergic bronchopulmonary aspergillosis
Granulomatosis with polyangiitis (Wegener's)
Lupus pneumonitis
Hypersensitivity pneumonitis
Others (thromboembolic pulmonary manifestations, psittacosis)

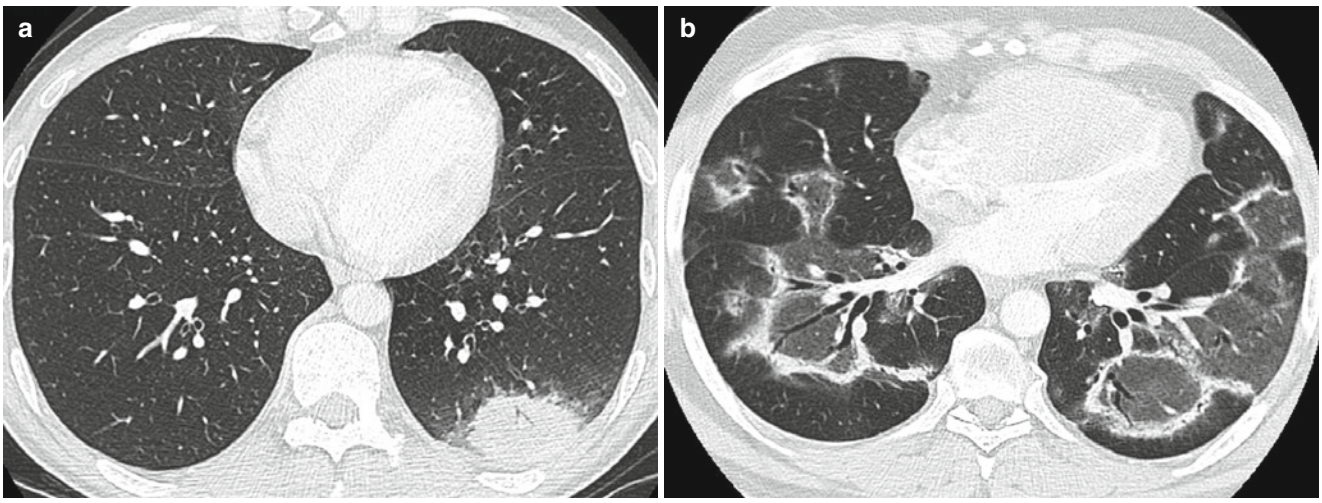

Fig. 24.4 (**a**) Isolated nodular form of organizing pneumonia: unique dense rounded mass with irregular margins located in the left lower lobe. (**b**) Reverse halo sign in organizing pneumonia: multifocal opacities characterized by dense margins and central ground glass opacities with air bronchogram. This feature is not specific and may be found in other inflammatory and infectious disorders

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, 22, 26, 33, 44], some presenting with severe, rapidly progressive disease and respiratory failure [23, 45–51]. Some cases were associated with drugs, connective tissue diseases, or toxic exposure [50–52], whereas other appeared cryptogenic [23, 46, 47, 52].

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. Hence, 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 [53, 54]. 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 [54], and that OP/NSIP overlap might explain part of the diffuse infiltrative cases of OP [55]. Hence, patients presenting at imaging with both interstitial changes (histologically corresponding to NSIP) and consolidations (histologically corresponding to OP) have been reported [56]. 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 [54]. 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 CT follow-up reported the evolution of OP consolidations into reticular changes resembling NSIP pattern in a subset of patients [57]. The coexistence of OP and NSIP histological patterns at surgical lung biopsy has been especially observed in idiopathic inflammatory myopathies, in contrast with other autoimmune diseases [58], but more histological data are needed to support the concept of OP/NSIP overlap as a distinct entity.

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 DAD 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 [59] (see below).

Finally, other cases initially reported as diffuse OP may have had acute exacerbation of interstitial lung disease, a recently described acute event occurring in the natural history of idiopathic pulmonary fibrosis, NSIP and other fibrotic interstitial disorders [60]. Acute exacerbations of interstitial lung disease have been associated with histological patterns of either OP or DAD at lung biopsy, the former being associated with a much better short term prognosis [61].

Although genuine diffuse infiltrative OP probably exists, it still awaits better characterization and distinction from similarly appearing entities. 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 [62–65], a micronodular pattern, with multiple small well- or poorly- defined nodules, or nodules with an air bronchogram [66]. Other variants include a bronchocentric pattern, a perilobular pattern resembling thickened interlobular septas, circumferential subpleural linear opacities, and radial opacities [32, 62, 66–69]. 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. 24.4b) [66]. Contrary to early beliefs, this sign is not specific to OP and may also be found in Churg-Strauss syndrome, granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), chronic eosinophilic pneumonia, lymphomatoid granulomatosis, tuberculosis, and various fungal infections [70].

Histopathological Diagnosis of OP Pattern

Buds of granulation tissue (Masson's 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. 24.1). Associated features include mild interstitial inflammatory infiltrate, type II cell hyperplasia, and intraalveolar 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, tumors, pneumonia distal to airway obstruction, hypersensitivity pneumonitis, NSIP, chronic idiopathic eosinophilic pneumonia, or GPA (Wegener's) [11, 12, 71] (Table 24.3). For instance, OP pattern has been found in the vicinity of tumoral tissue in up to 40 % of resected lung cancers [72]. 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 24.1) [3, 11]. The main differential diagnosis of OP pattern at histopathology includes NSIP and the organizing stage of DAD [3].

Table 24.3 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 (Churg-Strauss)
Granulomatosis with polyangiitis (Wegener's)
Primary pulmonary lymphoma
Diffuse alveolar damage
Drug reactions and toxic exposures
Others

Clinicopathological Diagnosis of OP Syndrome

The clinicopathological 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 active 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 [73]. 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 [74]. 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 [74]. A sensitivity of 20 % and a specificity of 89 % were found in another study using the same criteria [36]. 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 [74]. Although generalization of these data is questionable, expert opinion-based current international guidelines consider that if the clinical and imaging picture is typical with multifocal opacities, a TBB showing also typical intraalveolar buds of granulation tissue is sufficient to confidently diagnose OP [3, 55].

Box 24.1
Diagnostic Criteria of Organizing Pneumonia

A. Compatible clinical picture, imaging and bronchoalveolar lavage (see text)
B. OP pattern at histopathology obtained by transbronchial, transthoracic, or surgical lung biopsy*, 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

*Modifying circumstances:

1. A diagnosis of OP without biopsy is acceptable if a typical clinico-radiological picture and a well-identified cause are present, and if an infectious process has been ruled out
2. If the patient is too frail or too old for a biopsy, an empirical treatment 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
3. If corticosteroids are administered empirically, a critical re-assessment 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

Adapted from Ref. [3]

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 is recommended to make sure that OP is the dominant histopathological pattern and not just an ancillary finding in the frame of another pathological process (Fig. 24.5a) [73].

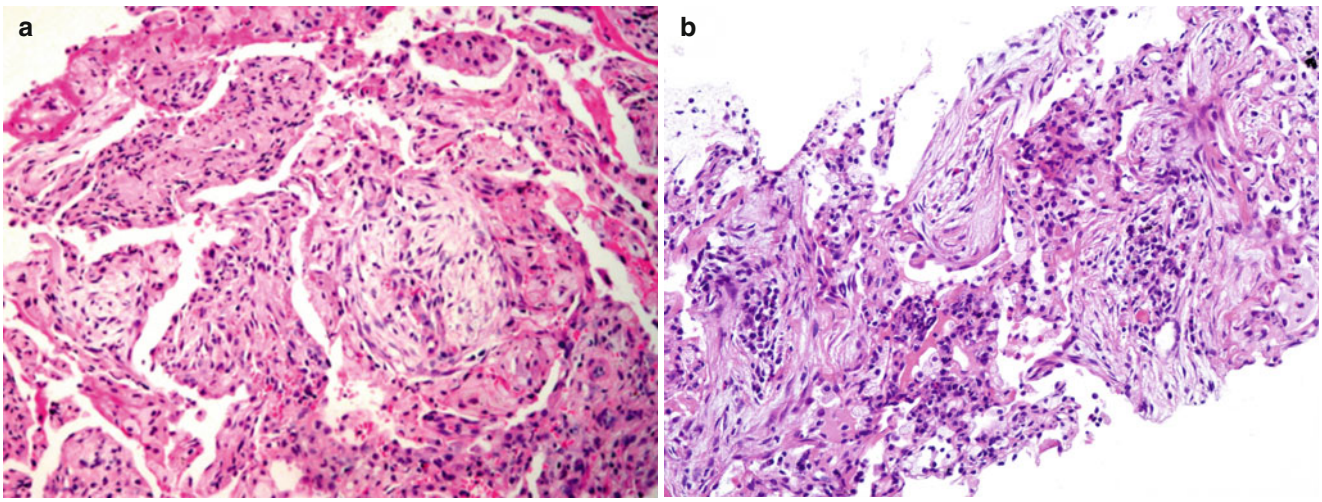

Fig. 24.5 (**a**) Transbronchial biopsy showing a few buds of granulation tissue filling alveolar spaces, with moderate lymphocytic inflammatory infiltrates of the alveolar walls, in a patient with diffuse parenchymal ground glass opacities. Organizing pneumonia was initially diagnosed, but surgical lung biopsy showed a pattern of nonspecific interstitial pneumonia, in which organizing pneumonia was only an ancillary feature. (**b**) CT-guided transthoracic needle biopsy in organizing pneumonia. Numerous intraalveolar buds of granulation tissue with fibroblasts and inflammatory cells embedded in a loose myxoid matrix are visible

Transthoracic CT-guided needle biopsy has been recently reported as a useful minimally invasive diagnostic method for OP with a high diagnostic yield [75, 76]. Most patients studied had unilateral or bilateral consolidations or tumor-like lesions, and only a few had a diffuse infiltrative pattern [75, 76]. The most frequent complications were subclinical 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. 24.5b). 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 of a biopsy, and this strategy deserves further studies [36]. If the risk/benefit ratio of lung biopsy is considered unfavorable due to old age, frail patient or significant comorbidities, a presumptive diagnosis of OP and an empirical treatment 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. Hence, disorders mimicking the clinical and imaging features of OP may initially respond to corticosteroid treatment, including GPA (Wegener's), 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 (formerly bronchoalveolar carcinoma), eosinophilic pneumonias (either idiopathic or secondary to a known cause), GPA (Wegener's), Churg-Strauss syndrome, 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, 71]. Although the latter usually consist of small foci of OP at the vicinity of otherwise typical granulomatous lesions, OP pattern may occasionally be a prominent histological finding in GPA [11, 71].

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, other idiopathic interstitial pneumonias, and acute exacerbation of pre-existing interstitial lung disease.

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 [27], 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 24.4) [27, 73]. 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 [73]. 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 [77]. 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 [78–80]. OP can also occur during myelo- or lymphoproliferative syndromes, and after lung or bone marrow transplantation. In the latter, an association has been recently 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 [81].

OP may occur in women receiving radiation therapy for breast cancer [82–87], with a reported incidence of 1.8 % among 2,056 patients followed by chest-X-ray every 3 months for 1 year [86]. Affected patients 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 [82]. 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 controlateral lung. Opacities may be migratory. BAL shows a typical mixed pattern alveolitis. The outcome is favorable under corticosteroid treatment [82]. Despite the frequent occurrence of relapses, a complete cure is usually observed. In milder cases, spontaneous disappearance without corticosteroids has been reported [88]. Interestingly, this variant of OP has been almost exclusively described in women irradiated for breast carcinoma, and only rarely in individuals of both genders irradiated for other types of tumors, especially lung cancer. The particular tangential

Table 24.4 Causes of secondary organizing pneumonia, with relative frequencies of main categories

Infections	**~45 %**
Bacteria (*Chlamydia pneumoniae*, *Coxiella burnetii*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Nocardia asteroides*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus aureus*, *Streptococcus group B*, *Streptococcus pneumoniae*), **virus** (*herpes virus*, *human immunodeficiency virus*, *influenza*, *parainfluenza*, *adenovirus*, *cytomegalovirus*, *hepatitis C*), **parasites** (*Plasmodium vivax*), **fungi** (*Cryptococcus neoformans*, *Penicillium janthinellum*, *Pneumocystis jiroveci*)	
Drugs	**~20 %**
5-Aminosalicylic acid, amiodarone, amphotericin, azathioprine, barbiturates, beta blockers, bleomycin, busulphan, carbamazepine, cephalosporin, clomipramine, cocaine, erlotinib, everolimus, gold salts, interferon, L-tryptophan, mesalazine, minocycline, nitrofurantoin, nilutamide, oxaliplatin, phenytoin, rituximab, sulfasalazine, tacrolimus, thalidomide, temozolomide, ticlopidine, transtuzumab. **See also** www.pneumotox.com	
Solid tumors and hematologic malignancies	**~15 %**
Autoimmune/inflammatory disorders	**~11 %**
Systemic lupus erythematosus, Behçet disease, rheumatoid arthritis, polymyalgia rheumatica, polymyositis and dermatomyositis, systemic sclerosis, mixed connective-tissue disease, Sjögren syndrome, ankylosing spondylitis	
Radiation therapy for breast carcinoma	**~9 %**
Allografts (lung, bone marrow, kidney, liver)	
Inflammatory bowel diseases	
Toxic exposures (acramin FWN – an aerosolized textile dye, paraquat, sulfur dioxide, house fire, paraffinic mineral oil)	
Post-obstructive pneumonia and aspiration pneumonia	
Other	
IgA nephropathy, thyroiditis, primary biliary cirrhosis, mesangiocapillary glomerulonephropathy, Sweet's syndrome, common variable immunodeficiency, essential mixed cryoglobulinemia, coronary artery bypass graft surgery	

From Ref. [27]

irradiation fields used for breast cancer could play a role. 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 [89]. Hormonal factors could also be involved. Hence, in one study, age >50 and anti-estrogen therapy were significantly correlated with the occurrence of OP, with odd ratios of respectively 8.88 and 3.05 [87]. However, given the importance of hormonal therapy for tumor control in these patients, avoidance or interruption of hormonal therapy to prevent or cure OP cannot be recommended at the present time.

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 [41], others have reported underlying COPD in up to 67 % of cases, and recurrent respiratory infections in up to 57 % [40], 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 [42]. Aspiration of food particles may be another cause of focal OP [90]. 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 [90]. Twenty-two percent of these cases presented as solitary nodules suspect of lung cancer, whereas food aspiration was clinically suspected in less than 10 % [90]. Infraclinical particulate matter aspiration pneumonia may thus be a relatively common cause of lung nodules presenting with OP pattern at histopathology. Interestingly, the prevalence of active or former smoking appears high in series of isolated nodular OP (57–93 %) [39–43]. It is currently unknown whether smokers are more prone to develop this presentation of OP, or are simply more likely to undergo a surgical procedure for such nodular lesions resembling lung cancer.

In the majority of cases, OP has no recognizable cause [23] 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 major idiopathic interstitial pneumonias (acute/subacute disorders) [4].

Treatment

Corticosteroids are the current standard treatment of OP [2, 14, 20, 22, 26, 31, 34], although spontaneous improvement has occasionally been reported [2, 88]. 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 [21, 22]. 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 [22, 55]. 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 % [22]. In an attempt to better define the corticosteroid treatment in COP, a standardized therapeutic regimen has been proposed by the French Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires (Table 24.5) [22]. A retrospective comparison of patients having received this standardized protocol with a group treated with other therapeutic regimens did not reveal any differences in terms of efficacy, delay to remission, occurrence of relapses, morbidity, or final outcome [22]. In contrast, cumulated doses of prednisone after 1 year were reduced twofold in the group having received the standardized treatment [22]. 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 [47–49] and immunosuppressive treatment with cyclophosphamide, azathioprine, or cyclosporin A have been used [46, 50, 51, 91, 92], especially in acutely ill patients who do not improve within a few days of corticosteroid treatment. However, the efficacy of these strategies is not established. Whether the patients requiring immunosuppressive drugs in addition to prednisone had more frequently a diffuse infiltrative pattern than a multifocal pattern at imaging is unclear, as detailed chest CT scan analysis was not available in most of these cases.

Whether SOP should be treated differently from COP is currently unclear. Some data suggest that SOP is associated with less frequent resolution of symptoms and higher mortality than COP [26], but no such difference was found in another recent large series [27]. In a recent comparison of COP and OP secondary to connective tissue disease, treatment modalities, improvement rate and mortality rate were similar, although complete recovery was slightly more frequent in COP [93]. Thus, at the present time, no data support the use of different treatment regimens for SOP and COP.

Not all cases of OP require treatment. In six large series totalizing 418 cases [2, 23, 27, 31, 52, 93], 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 [23, 52, 93]. In another study of 12 women with OP after radiation therapy for breast cancer detected by systematic chest X-ray, only 6 were symptomatic. Hormonal treatment was temporarily withheld in 9, and complete cure was observed in all without corticosteroids [88]. 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.

Several macrolide antibiotics (erythromycin, clarithromycin, azithromycin) have been found to have anti-inflammatory properties, which have been first observed in Japanese panbronchiolitis. A significant clinical benefit of azithromycin has now been demonstrated by randomized controlled trials in several other airway diseases including cystic fibrosis, bronchiolitis obliterans syndrome after lung transplantation, bronchiectasis, and more recently COPD. A beneficial effect of erythromycin and clarithromycin has also been reported in small uncontrolled series of COP and OP secondary to radiation therapy for breast cancer [94–97]. In a retrospective series of 12 patients with mild or moderate OP, the administration of clarithromycin 1,000 mg/day for 3–4 months led to complete cure in 7 cases, and an improvement in 2, whereas 3 other patients did not respond and required prednisone as a rescue therapy [97, 95]. Altogether, in the cases reported so far, onset of clinical improvement with macrolides appeared much slower than with corticosteroids (weeks instead of days) and therapeutic response was less constant [94–97]. Given the current paucity of evidence, the use of macrolides for the treatment of OP is currently not recommended in the usual clinical setting.

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 [22]. In a minority of cases, some minor fibrous sequellae can persist at imaging. Overall mortality in COP is reported to be <5 % [22, 23]. It has been suggested that the prognosis could be less favorable in SOP than in COP [2, 13, 26, 50], but a recent formal comparison did not find any significant difference between COP and SOP in clinical features, response to therapy, relapses and outcome [27].

COP is characterized by the frequent occurrence of relapses when corticosteroid treatment is tapered or stopped [1, 2, 14, 22]. Single or multiple relapses have been reported in up to 58 % of cases [22]. 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 [22]. Relapses are not due to insufficient prednisone dose for the initial episode, but delayed treatment onset could be a risk factor [22]. Other factors associated with the occurrence of relapses include more severe hypoxemia at first examination [98], elevation of serum gamma-glutamyl-transferase and alkaline phosphatase [22], and the multifocal form of OP [99]. Importantly, relapses did not affect morbidity and mortality [22]. 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, and even multiple 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 was initially recommended, but they now appear as a relatively benign phenomenon, which can usually 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 24.5), starting at 20 mg/day of prednisone [22]. In localized OP, relapses are less common [40, 41], 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 [23, 46, 47, 50–52]. Some of these cases were secondary to collagen vascular diseases, drugs, or toxic exposure to an aerosol textile dye [50–52] and others were idiopathic [23, 46, 47, 52]. In the 44 cases from five series with available data [46, 47, 50–52], nearly all patients received high-dose corticosteroids, 32 % received immuno-

Table 24.5 Proposed therapeutic regimen for typical COP

Step	Duration (weeks)	Doses of prednisone for the initial episode	Doses of prednisone for the first relapse (mg/day)
1	4	0.75 mg/kg/day	20
2	4	0.5 mg/kg/day	20
3	4	20 mg/day	20
4	6	10 mg/day	10
5	6	5 mg/day	5

Adapted from Ref. [22]

suppressive drugs (mostly cyclophosphamide), and 43 % required mechanical ventilation. Twenty-seven percent recovered, 9 % evolved to chronic respiratory insufficiency or required lung transplantation, and 64 % died. Factors which have been associated with a poorer outcome in OP include presence of collagen vascular disease [50], diffuse infiltrative pattern at imaging [14, 100], absence of lymphocytosis at BAL [14, 50], and interstitial fibrosis with architecture remodeling of lung parenchyma at histopathology [46]. As several of these characteristics are atypical in OP, it is possible that some of these cases had in fact other disorders in which OP pattern was only an ancillary histological finding, such acute interstitial pneumonia, acute respiratory distress syndrome, acute exacerbation of interstitial lung disease, or acute fibrinous and organizing pneumonia (see below). Alternatively, some cases may have had a true overlap between OP and one of these entities. Hence, among ten patients with severe OP and characteristic OP pattern at lung biopsy, seven died and five of them had associated UIP pattern, honeycombing or DAD at autopsy [50]. 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. Both multifocal and diffuse infiltrative imaging patterns have been described in severe OP [52].

Acute Fibrinous and Organizing Pneumonia

Acute fibrinous and organizing pneumonia (AFOP) has been first described in 2002 as an entity with overlapping features of DAD and OP [59]. 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 [59], 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 co-morbidities resulting in altered immunity (Table 24.6). Other cases were idiopathic. Most frequent chest X-ray features included bilateral basal and diffuse opacities, but detailed chest CT 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. 24.6a), and leading to recovery. The overall mortality rate was 53 %, which was similar to adult respiratory distress syndrome 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 the alveolar spaces with a conspicuous patchy distribution and a relatively normal intervening lung parenchyma. OP pattern with buds of fibroblasts within airspaces was present in all cases, but was usually less abundant than the intra-alveolar fibrin (Fig. 24.6b). Associated features included mild to moderate interstitial infiltrate with edema, predominant lymphocytes, sparse neutrophils, and type 2 pneumocyte hyperplasia. There were no hyaline membranes, abcesses, or granulomas. No histological characteristics were found predictive of outcome. The histopathological features of AFOP are summarized in Table 24.7.

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

Table 24.6 Conditions associated with acute fibrinous and organizing pneumonia

Infections
Haemophilus influenzae, *Acinetobacter baumanii*, severe acute respiratory syndrome coronavirus, *Pneumocystis jiroveci*, human immunodeficiency virus
Drugs
Abacavir, amiodarone, busulfan, decitabine
Autoimmune disease
Polymyositis, dermatomyositis, ankylosing spondylitis, systemic lupus erythematosus, primary biliary cirrhosis
Tumors
Lymphoma, acute lymphocytic leukemia
Environmental exposures
Construction worker, animal exposure (zoologist), excessive hair-spray use, coalminer
Allografts
Hematopoetic stem cell transplantation
Other
Renal failure
Idiopathic

Adapted from Ref. [59] and pneumotox.com

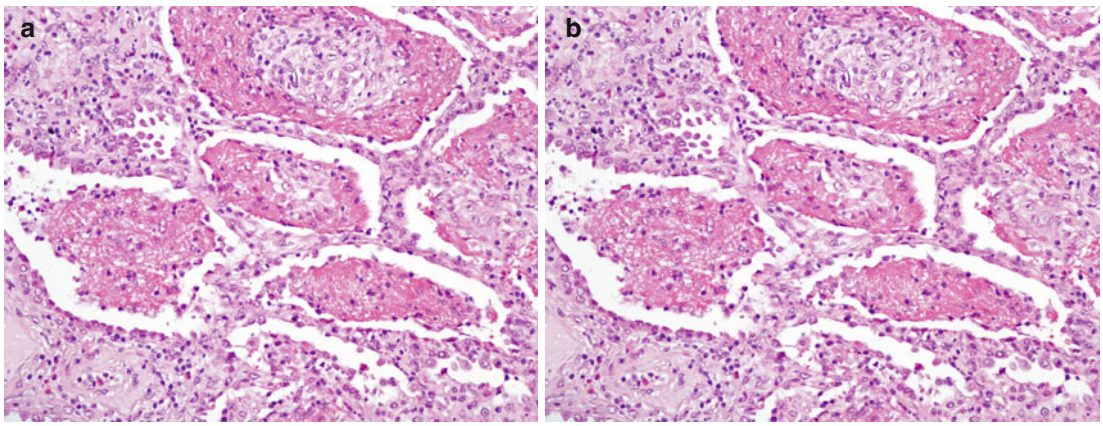

Fig. 24.6 Acute fibrinous and organizing pneumonia in a 68-old woman with symptoms of several month duration and lack of response to empirical antibiotic therapy. (**a**) Multifocal alveolar opacities with air bronchogram predominant at the lung bases. (**b**) Surgical lung biopsy showing prominent fibrin clusters filling alveolar spaces, with a lesser component of fibroblasts and inflammatory cells

Table 24.7 Histopathological features of acute fibrinous and organizing pneumonia

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 abcesses
Granulomatous inflammation

Adapted from Ref. [59]

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 [59]. 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 abcesses, necrotizing granulomas, GPA (Wegener's) lesions, and lung carcinomas [59]. 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 and outcome [59]. 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 [101]. The usefulness of cyclophosphamide and mycophenolate mofetil in addition to corticosteroids has been occasionally reported [102, 103]. Similarly to classical COP, relapses have been reported in AFOP [101].

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 treatment should be attempted after having ruled out or treated an infectious process.

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Interstitial Lung Disease in Systemic Sclerosis

25

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Introduction

In systemic sclerosis (SSc), cardiopulmonary involvement, consisting of interstitial lung disease (SSc-ILD) and pulmonary hypertension (SSc-PH) are now 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 hemorrhage 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 prevalence of SSc is 50–300/million [1]. SSc-ILD is present in over 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 5,800 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 3:1–14:1) aged 30–50 years [1]. In USA series, the risk of SSc-ILD increases in association with African American ethnicity, with severe SSc-ILD linked to male gender and cardiac involvement by SSc [4–6].

In autopsy studies of patients with SSc, interstitial lung disease is present histologically in most patients [7]. All histological patterns seen in the idiopathic interstitial pneumonias [8] have been reported in SSc-ILD [9], apart from pleuroparenchymal elastosis (which has been recognized only very recently and has yet to be wholly clinically characterised). However, the relative prevalence and prognostic significance of histological patterns differs greatly between idiopathic disease and SSc-ILD. In idiopathic interstitial pneumonia, the most prevalent histologic pattern is usual interstitial pneumonia (UIP), corresponding to idiopathic pulmonary fibrosis (IPF) [10]. IPF has a strikingly worse outcome than other idiopathic disorders, including fibrotic nonspecific interstitial pneumonia (NSIP) [10]. By contrast, NSIP is the most prevalent histologic pattern at biopsy and autopsy in SSc-ILD (Fig. 25.1). In a series of 80 SSc-ILD patients undergoing a diagnostic surgical biopsy [11], cellular or fibrotic NSIP (Figs. 25.1 and 25.2) was present in 78 %, with less than 25 % of patients having predominantly reversible disease. Infrequent histopathologic patterns included usual interstitial pneumonia (UIP) in 8 % and "end-stage lung disease" in 8 %. 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

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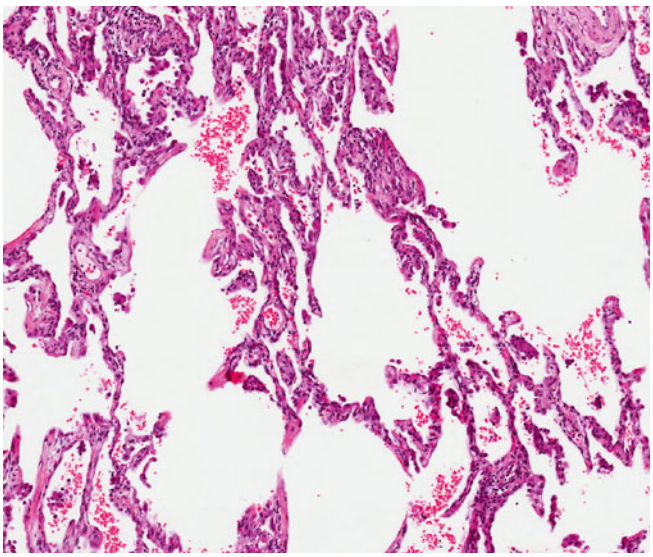


Fig. 25.1 Cellular NSIP. The lung shows diffuse involvement of the alveolar interstitium by a mild chronic inflammatory infiltrate

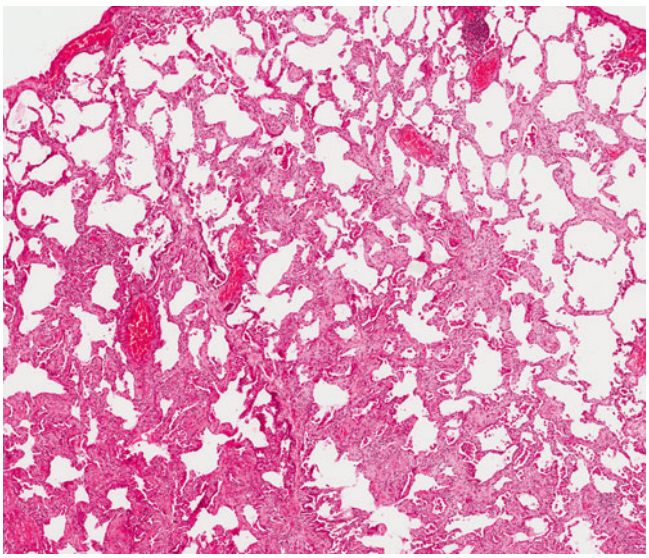


Fig. 25.2 Fibrotic NSIP. The lung shows diffuse involvement of the alveolar interstitium by a homogenous fibrosis with minimal inflammation. No fibroblastic foci were seen at high power (H&E stain ×10 magnification)

during follow-up. These findings are broadly compatible with outcome data in smaller series, although in one report, UIP appeared to be a malignant prognostic determinant [12].

High resolution computed tomography (HRCT) is the primary means of detecting SSc-ILD. 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 [13, 14]. HRCT appearances are typically compatible with NSIP, with prominent ground-glass attenuation and a low prevalence of honeycomb change [15]. HRCT has a high 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 multi-disciplinary 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 [16–18], and especially by recent HRCT data [19, 20].

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. In one series, SSc-ILD was identified in 53 % of patients with diffuse disease but in only 35 % of patients with limited disease [21].

It is likely that these observations reflect linkages to autoantibody status. 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 Scl-70 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 ten-fold 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]. 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 [29]. Other polymorphisms linked to SSc-ILD have included the IL-1α and IL-1β genes [30, 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 anemia, 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's 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. Recently, aspiration due to gastro-esophageal regurgitation (GER) has been recognized as a potential trigger of SSc-ILD. 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 dyspnea.

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, PFT 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 and 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, 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 hypocapnoea (reflecting alveolar hyperventilation). The performance of arterial gases can generally be avoided in routine evaluation as simple oximetry is an adequate substitute, although sometimes confounded by Raynaud's 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 dyspnea 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 on room air may allow the clinician to conclude that exercise tolerance is limited by extra-pulmonary factors such as musculoskeletal disease or lack of fitness. The six minute 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] although useful as a screening tool. HRCT findings closely resemble those seen in idiopathic NSIP [15] typically consisting of a variable mixture of ground-glass attenuation and reticulation (Fig. 25.2). 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. 25.3a). However, in the great majority of cases, ground glass is admixed with reticulation and there is traction bronchiectasis (Fig. 25.3b), 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 moni-

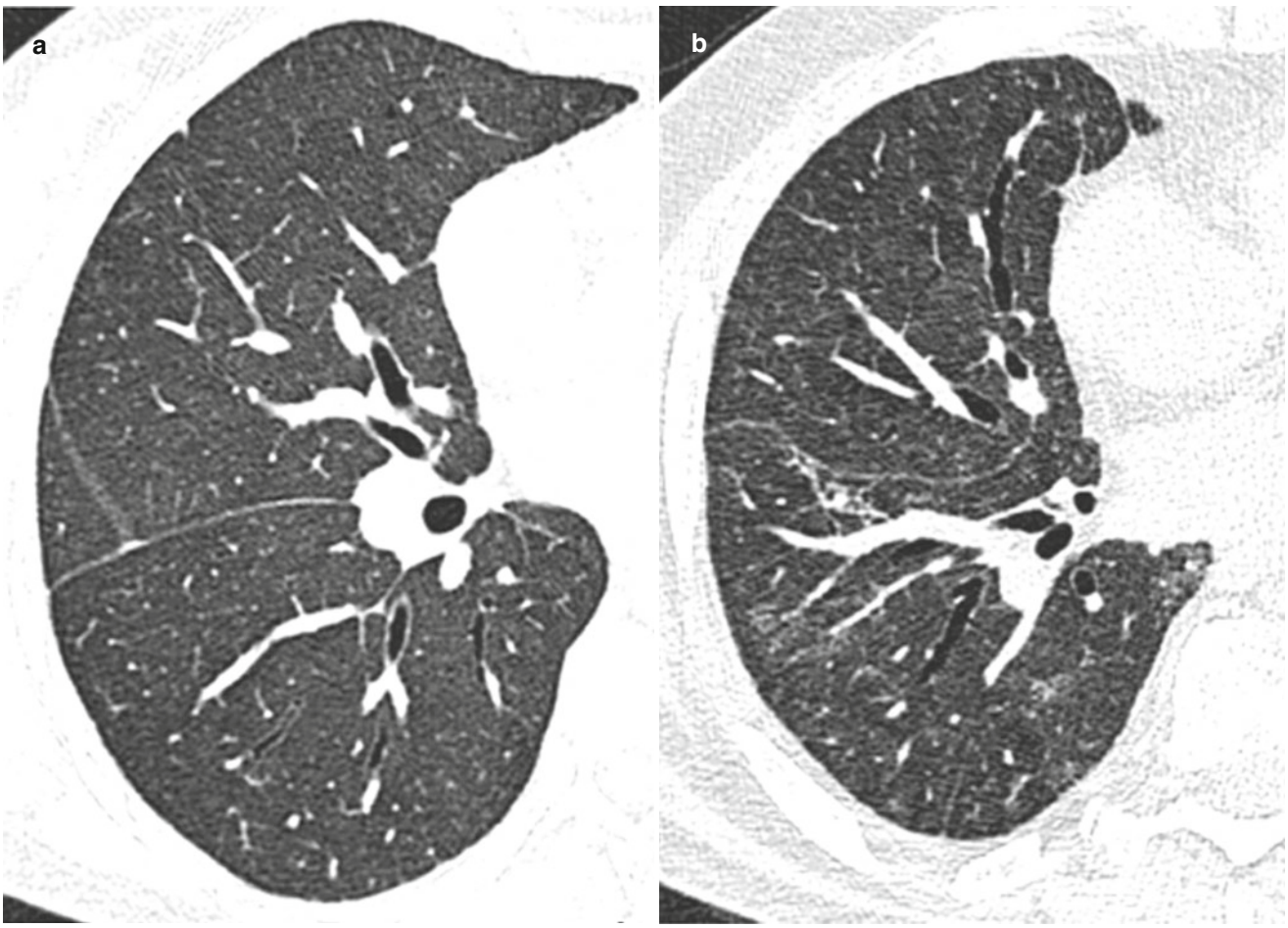


Fig. 25.3 (**a**) HRCT appearances in a patient with biopsy-proven cellular NSIP. There is a diffuse increase in lung attenuation without admixed reticulartion or traction bronchiectasis. (**b**) HRCT appearances in a patient with biopsy proven fibrotic NSIP. The diffuse increase in attenuation on HRCT represents fine fibrosis, with the presence of obvious traction bronchiectasis an important clue that interstitial disease was likely to be irreversible

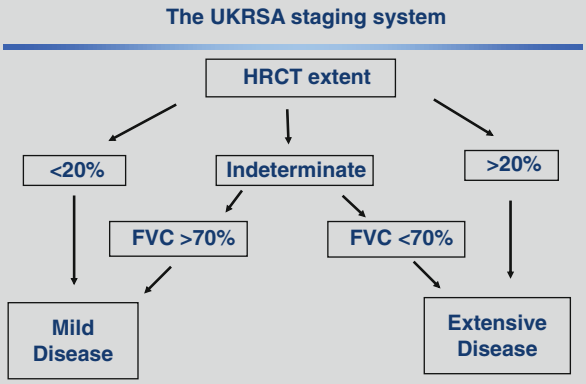
toring protocol is difficult to justify. Serial HRCT should only be performed on a case by case basis to answer specific clinical questions, with the most frequent scenarios being discordance between symptomatic change and pulmonary function trends and disproportionate decline in measures of gas transfer, 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 [20]. 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 25.1, 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 %. These thresholds

Box 25.1
The mild/extensive severity staging system for prognostic evaluation in SSc-ILD. Extensive disease is associated with an increase in mortality of over three-fold and a much higher likelihood of disease progression in the next year.



were very similar to HRCT and FVC thresholds in the Scleroderma Lung Study (SLS), below which treatment effects with oral cyclophosphamide were seen [19]. The two studies establish that the staging of severity using HRCT and FVC data is likely to be useful in informing treatment decisions in clinical practice. However, it should also be stressed that despite its prognostic utility, the Goh staging system has yet to be integrated into a validated management algorithm.

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.

Lastly, 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, the exact value of recent disease progression as a malignant prognostic determinant has yet to be quantified in clinical series. However, recent disease progression has been predictive of increased mortality in other forms of interstitial lung disease (most widely studied in idiopathic pulmonary fibrosis) [42]. Intervening to stabilize disease that is overtly progressive is warranted on simple commonsensical grounds.

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, 3–6 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. At present, no such biomarker is exists. Rapid clearance of inhaled technetium-labeled diethylene-triamine-pentacetate (^{99m}Tc-DTPA) from the lungs (a marker of increased alveolar cell permeability) is associated with a shorter time to decline in FVC in SSc-ILD, before and after adjustment for disease severity [43]. As this test is not widely available and the associated radiation burden is significant, substitute serum biomarkers are needed to detect lung epithelial damage. Attention has focused on two lung glycoproteins, KL-6 and SP-D in SSc-ILD [44–46] but the utility of these and other candidate biomarkers in routine practice is uncertain. With regard to non-epithelial biomarkers, IL6 was evaluated in a large retrospective study of SSc-ILD patients, including over 200 patients in a separate "test cohort". Increased serum IL6 levels were associated with more rapid disease progression, especially in mild disease [47].

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-recognised association between the presence of a BAL neutrophilia 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 [48]. 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 [49]. Following these studies, BAL is now performed much less frequently 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 millenium, multi-centre treatment studies in SSc-ILD have proven to be possible. Placebo-controlled trials of oral cyclophosphamide [19], intravenous cyclophosphamide [50] and bosentan [51] have now been completed.

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 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 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) [50]. 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 trial, although 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 [52].

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 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 trial had completed treatment and returned to routine follow-up, less than 15 % were prescribed open therapy by their primary physicians [53]. Crucially, there was no treatment effect in the SLS 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 [19].

At the time, it came as a surprise that in both trials, the treatment effect mostly represented stabilisation 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 stabilisation 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 [54]. Based on the reversibility of disease in these and other pilot series, BAL and HRCT findings considered to be indicative of "alveolitis" were entry criteria in the SLS study [19], although, as discussed earlier, reversible disease is identified reliably in SSc-ILD by neither test. Perhaps disease regression observed with cyclophosphamide therapy in early reports reflected the fact that open pilot interventions are commonly used selectively in patients with more rapidly progressive disease, in which major inflammation may be more prevalent. However, it appears from the controlled cyclophosphamide trials that in more typical lung disease, the primary treatment goal should be stabilisation of pulmonary fibrosis. This conclusion has been underlined by a meta- analysis of the effects of cyclophosphamide on pulmonary function, in which no significant improvement with treatment was seen [55]. In a further meta-analysis of 13 studies of non-advanced SSc-ILD, the primary outcome measures were change in FVC and DLCO [56]. Cyclophosphamide therapy was associated with stabilisation of FVC (but not DLco) at 12 months, although the conclusion that improvement was not evident was perhaps

undermined by the selection of an unrealistic cohort threshold for improvement (an average rise in FVC of at least 10 %) [56].

The SLS 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 [53]. No controlled data exist establishing the efficacy of "maintenance therapy", following initial induction with cyclophosphamide. Currently, clinicians tend to make a change, after 6–12 months, from cyclophosphamide to less toxic oral immunosuppressive agents, often in combination with low-dose corticosteroid therapy. For many years, azathioprine or methotrexate were used empirically. Recently, 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% [57]. Overall, mycophenolate mofetil was associated with stabilisation of disease, with no significant improvement in either pulmonary function variable. Importantly, no major side effects were observed . A recent retrospective study in over 100 patients with connective tissue disease-associated interstitial lung disease included a significant sub-group with SSc-ILD [58]. On average, disease stabilised with treatment and mycophenolate mofetil was tolerated well. A comparison of the efficacy and tolerability of mycophenolate mofetil and cyclophosphamide, undertaken by the USA SLS group has completed recruitment. In many patients with disease that is clinically significant but not severe, clinicians now choose to introduce mycophenolate mofetil at the outset, usually in combination with low dose oral corticosteroid therapy. However, this treatment algorithm has not been validated and the value added by low dose prednisolone has not been quantified.

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 [59, 60]. Other interventions have not been studied in detail in SSc-ILD. It might be supposed that anti-fibrotic agents with apparent treatment benefits in idiopathic pulmonary fibrosis [anti-oxidant therapy [61], pirfenidone [62] might also be beneficial in SSc-ILD. However, these agents have not been evaluated in SSc-ILD. A multicentre placebo-controlled trial of bosentan was definitively negative in SSc-ILD [51]. Bone marrow transplantation has been used in small groups of patients with severe SSc, including in some patients with severe SSc-ILD [63, 64]. However, although significant improvements in pulmonary function tests have occasionally been seen, this treatment approach is unlikely to become practicable as standard therapy in severe SSc-ILD.

Rituximab is more promising. In a pilot evaluation of anti-topoisomerase positive SSc-ILD patients, there were improvements in pulmonary function data initially [65] and further improvements at 2 years [66]. Uncontrolled treatment benefits have also been reported in patients with polymyositis lung [67] and in a mixed group of patients with connective tissue disease and life-threatening lung disease [68]. However, whether these findings can be extrapolated to the use of Rituximab as a more routine therapy in SSc-ILD will require controlled evaluation in larger patient cohorts.

Clinical Vignette

A case of a 71 year old man who presented with a 1 year history of Raynauds 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 routone 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 %, Kco 68 %. The calculated alveolar-arrterial oxygen gradient was at the upper limit of normal (3.1 kpa). An echocardiogram was unremarkable. Representative HRCT sections (Fig. 25.4a–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. 25.4b).

His initial lung-specific therapy consisted of Prednisolone 10 mg daily, intravenous cyclophosphamide 650 mg/m^2 at 4 weekly intervals. After six cycles of cyclophosphamide, he continued on low dose Prednsiolone and Azathioprine 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. 25.5a–c). It is instuctive to note that following a normal echocardiogram, serial Kco levels (Fig. 25.5b) provided the clearest signal of an increasing

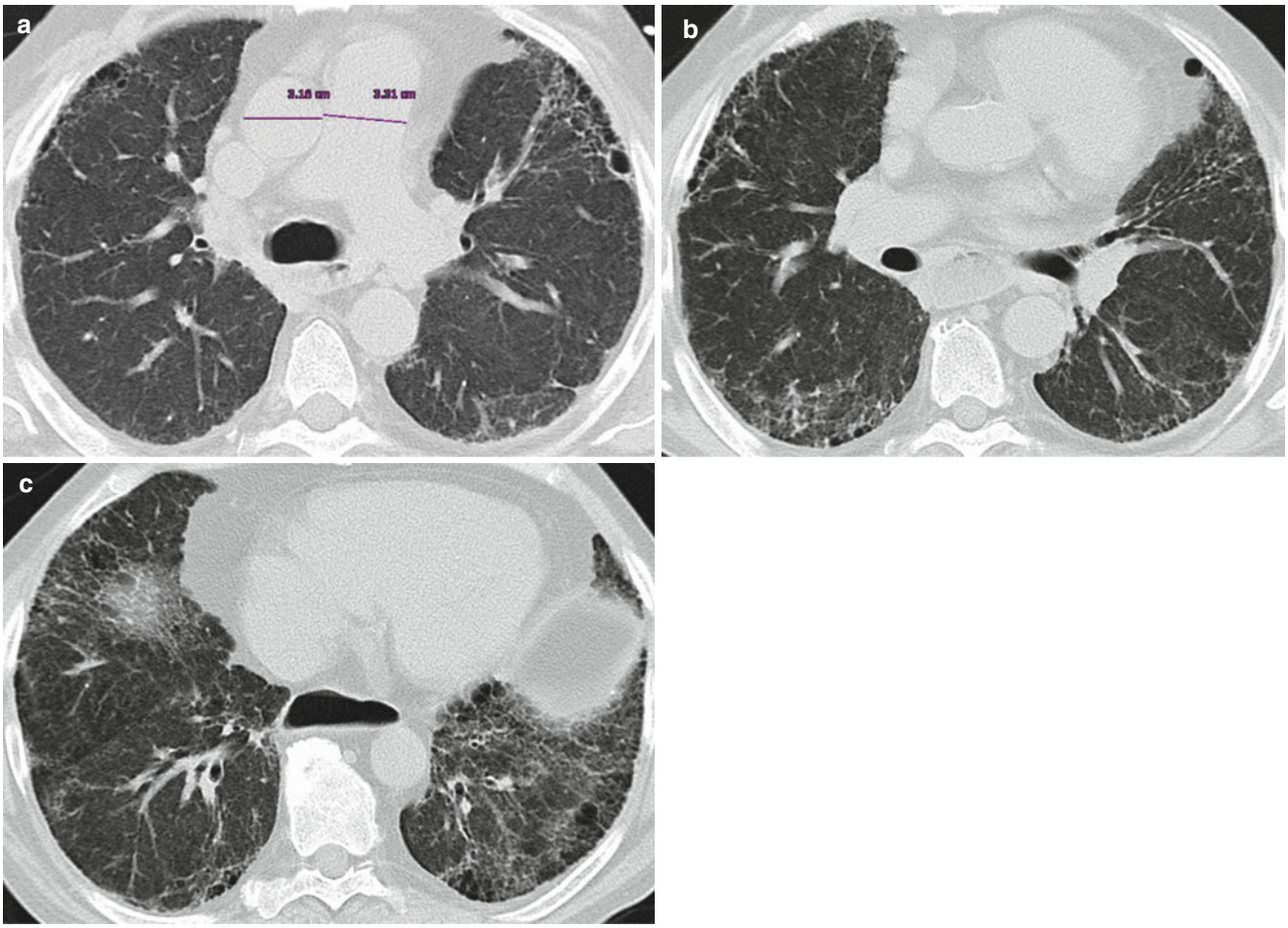


Fig. 25.4 (**a**–**c**) Representative HRCT sections in a patient who was staged as having extensive interstitial lung disease, based on an "indeterminate" disease extent and an FVC level of 60 % of predicted. In basal sections, disease extent on HRCT was clearer greater than 20 % but this was counter-balanced 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

pulmonary vasculopathy whereas DLco change (Fig. 25.5a) 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 Raynauds 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 immunmodulation, with complete stabilization of interstitial lung disease during 6 years of follow-up. The autoantibody profile was non-specific, possibly in keeping with the parallel development of interstitial lung disease and a disportionate pulmonary vasculopathy (in association with marginally extensive lung disease but bo 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 can not 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.

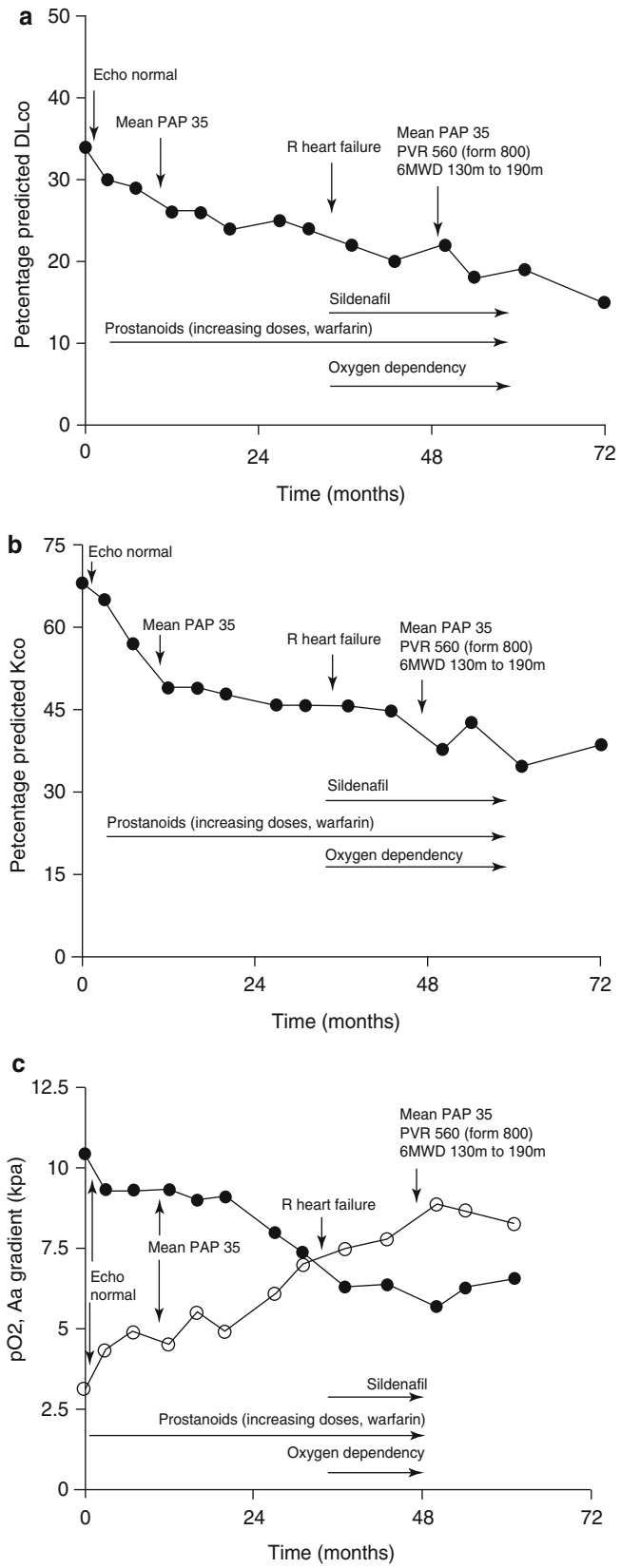


Fig. 25.5 Serial measures of gas exchange and gas transfer throughout follow-up are shown, including DLco (**a**), Kco (**b**) and pO2 and calculated alveolar-arterial oxygen gradient on air (**c**). Serial trends are shown in relation to relevant therapies and findings at echocardiography and right 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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Interstitial Lung Disease in Connective Tissue Diseases Other Than Systemic Sclerosis

26

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The connective tissue disorders (CTD, also called collagen vascular diseases) represent an heterogenous group of immunologically mediated inflammatory disorders with a large variety of affected organs besides the lungs. The respiratory system may be involved in all its components: airways, vessels, parenchyma, pleura, respiratory muscles, etc.… The frequency, clinical presentation, prognosis and response to therapy vary, depending on the pattern of involvement as well as on the underlying connective tissue disorders. The subject of this article is to review the interstitial lung disease (ILD) observed in patients with CTD. We will focus on the most frequent CTD: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren's syndrome (SS), inflammatory myopathies and mixed connective tissue disease (MCTD). Systemic sclerosis and undifferentiated connective tissue disease will not be touched as these diseases are developed in specific chapters of this book.

Systemic Lupus Erythematosus

Systemic lupus erythematosus is an autoimmune disorder which primarily affects women (see Table 26.1 for classification criteria). SLE may affect virtually any organ and as such, the respiratory system is frequently involved by the disease. The majority of patients with SLE develop pleural or pulmonary disease in the course of their illness. Respiratory involvement is more common in men than in women.

The American College of Rheumatology classification criteria for systemic lupus erythematosus (SLE) were updated in 1997 [1] and again in 2012 [2]. Although lung involvement is not a criterion for SLE diagnosis, lung involvement has been associated with increased mortality [3, 4]. The prognosis of SLE greatly improved in the past years. The results from two prospective cohorts of 1,000 European [5] and 644 Canadian [3] patients with lupus found 95 and 93 % 5-year survival rates, respectively.

Interstitial lung disease in SLE may be acute or chronic. This review will focus on specific involvement of the lung by SLE, however it must be kept in mind that infection is the main cause of lung infiltrates in SLE. The risk of pulmonary infection is three time higher in patients with SLE than in the general population [6]. As infections are among the most important causes of morbidity and mortality in patients with SLE, an aggressive approach to SLE patients with new pulmonary infiltrates is mandatory, and infection should be presumed and treated empirically until an alternative diagnosis is given.

Acute Lupus Pneumonitis

Acute lupus pneumonitis (Fig. 26.1) occurs in 1–4 % of SLE patients. It often reveals a previously unknown SLE (50 % of the patients in the series of Matthay et al. [7] or may occur in the course of the disease.

The clinical presentation is non specific, simulating an acute infectious pneumonia, with cough, dyspnea and fever. Hemoptysis is occasionally seen. Arterial blood gases analysis reveal hypoxemia with hypocapnia. Chest radiography and CT-scan show uni or bilateral alveolar infiltrates which usually predominate in the lower lobes. Small pleural effusions are commonly associated. Occasionally, acute respiratory failure, requiring mechanical ventilation will occur. A part from the rare occurrence of LE cells or the detection of

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Table 26.1 Systemic Lupus International Collaborating Clinics (SLICC) Classification criteria for Systemic lupus erythematosus [2]

A patient is classified as having SLE if he satisfies 4 of the clinical and immunologic criteria used in the SLICC classification criteria, including at least one clinical criterion and one immunologic criterion, OR if he or she has biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies.
Criteria are cumulative and need not be present concurrently.
Clinical criteria
1. Acute cutaneous lupus, including:
Lupus malar rash (do not count if malar discoid)
Bullous lupus
Toxic epidermal necrolysis variant of SLE
Maculopapular lupus rash
Photosensitive lupus rash
In the absence of dermatomyositis
OR subacute cutaneous lupus
2. Chronic cutaneous lupus, including:
Classic discoid rash, localized or generalized
Hypertrophic (verrucous) lupus
Lupus panniculitis
Mucosal lupus
Lupus erythematosus tumidus
Chillblains lupus
Discoid lupus/lichen planus overlap
3. Oral ulcers (palate, buccal, tongue) OR nasal ulcers *in the absence of other causes*
4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs)
5. Synovitis involving 2 or more joints
6. Serositis (Pleurisy or pericarditis)
7. Renal: urine protein-to-creatinine ratio (or 24-h urine protein) representing 500 mg protein/24 h OR red blood cell casts
8. Neurologic
Seizures
Psychosis
Moneuritis multiplex
Myelitis
Peripheral or cranial neuropathy
Acute confusional state
9. Hemolytic anemia
10. Leukopenia (<4,000/mm^3 at least once) OR Lymphopenia (<1,000/mm^3 at least once)
11. Thrombocytopenia (<100,000/mm^3 at least once)
Immunologic criteria
1. ANA level above laboratory reference range
2. Anti-dsDNA antibody level above laboratory reference range (or >2-fold the reference range if tested by ELISA)
3. Presence of Anti-Sm antibody
4. Antiphospholipid antibody positivity as determined by any of the following
(a) Positive test result for lupus anticoagulant
(b) False-positive test result for rapid plasma regain
(c) Medium- or high-titer anticardiolipin antibody level (IgA, IgG or IgM)
(d) Positive test result for anti-β2-glycoprotein I (IgA, IgG or IgM)
5. Low complement
(a) Low C3
(b) Low C4
(c) Low CH50
6. Direct Coomb's test in the absence of haemolytic anemia

hematoxylin eosin bodies, histological features obtained are non-specific and include alveolar wall damage and necrosis, alveolar edema, hyaline membranes, inflammatory cell infiltration and alveolar hemorrhage; capillary inflammation and thrombosis are also detected; deposits of immunoglobulins and complement are variably present [8, 9].

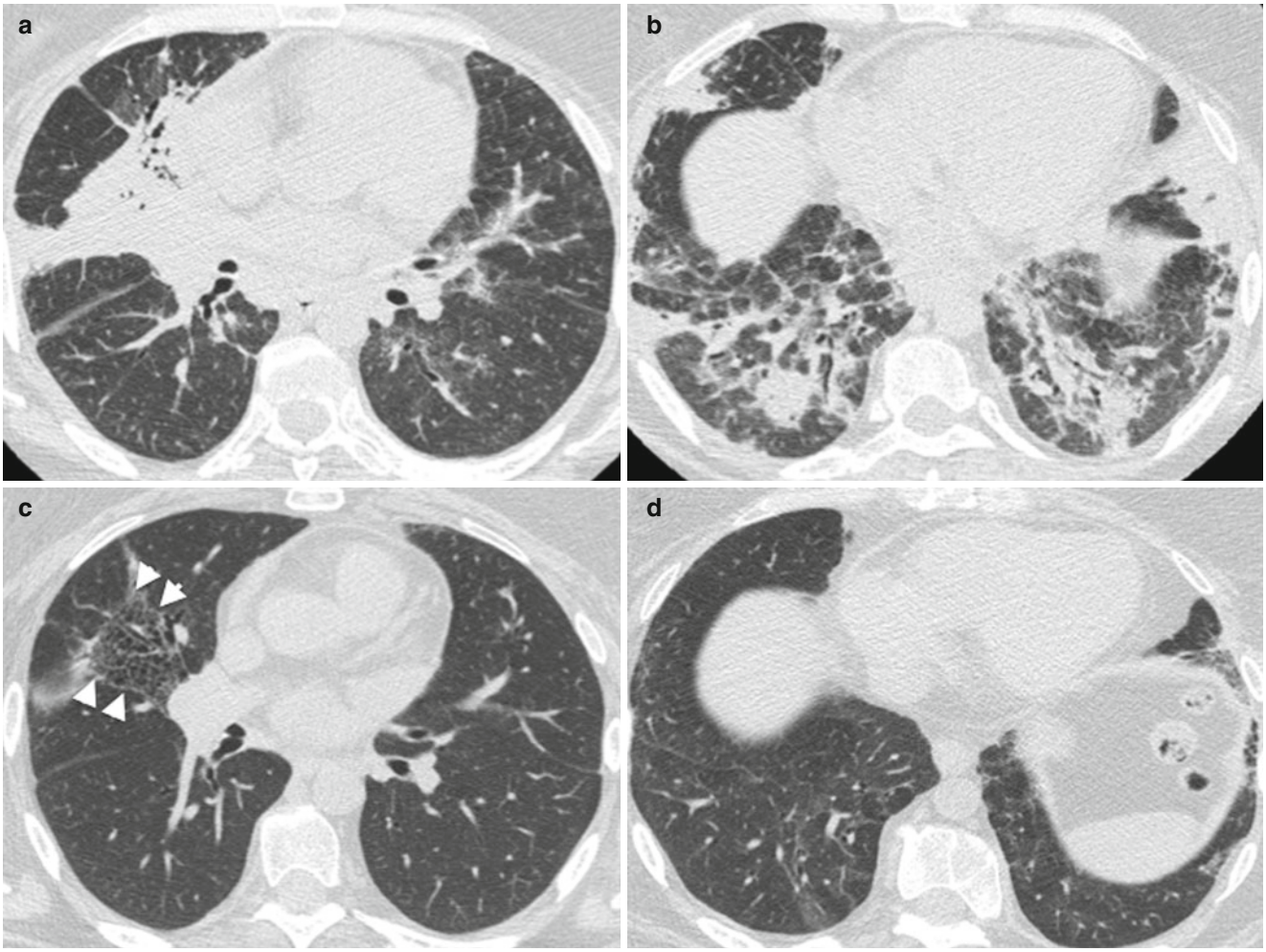

Fig. 26.1 Acute lupus pneumonitis revealed the systemic lupus erythematosus in a woman. High resolution computed tomography of the lungs showed areas of consolidation (panels **a**, **b**). After corticosteroid treatment, most of the opacities resolved (panels **c**, **d**). The right middle lobe was partly destroyed by residual fibrosis (panel **d**)

A syndrome of acute reversible hypoxemia with normal chest x-ray films, a normal CT scan and a rapid response to corticosteroids has been described in patients with SLE [10, 11]. The syndrome was attributed to leukoaggregation in the lung capillaries. Available histological data are very limited but demonstrate an infra-radiologic inflammation in the alveolar space [12]. This suggests that this syndrome is a less severe form of acute lupus pneumonitis rather than a distinct entity [12].

The clinicoradiographic presentation of lupus pneumonitis is absolutely non specific and may simulate lung infection, pulmonary embolism, or other acute pulmonary diseases. An invasive diagnostic workup must be set up and time is crucial since acute respiratory failure and death may develop. Bronchoalveolar lavage with a search for bacterial, viral, fungal and parasitic agents is required, but empirical antibiotherapy must not be delayed. CT-scan will appropriately characterize the lesions and exclude the potential diagnosis of pulmonary embolism. Lung biopsy has been advocated by some experts to exclude some diagnostics, however this procedure bears its own morbidity and mortality and lung histologic analysis is usually non diagnostic.

The treatment of acute lupus pneumonitis is based on case reports or small series. Empirical broad-spectrum antibiotic coverage should be maintained until infection is excluded. Mechanical ventilation and supportive intensive care may be required. The basis of drug therapy for acute lupus pneumonitis is high-dose corticosteroids (prednisone, 1–2 mg/kg/day) [13, 14]. Pulse methylprednisolone (250–1,000 mg/day for several days) have been used in patients with a severe initial presentation. Most patients will improve with this treatment despite 50 % mortality has been reported in older series [13, 14]. Cyclophosphamide, intravenous immunoglobulins, or plasma exchange may be used in cases of acute lupus pneumonitis refractory to corticosteroids. The place of

new immunomodulatory agents such as anti-TNF has not been evaluated [15].

Diffuse Alveolar Hemorrhage

Diffuse alveolar hemorrhage is a rare but severe manifestation of SLE, most series reporting 50–90 % mortality [13, 16, 17] although a more favourable outcome has been reported in recent series [18, 19]. Its prevalence ranges between <2 and 5.4 % of patients with SLE.

The pathogenesis of the disease is poorly understood. Immune complex-mediated injury, vasculitis with alveolar capillaritis, alveolar damage related to infection, probably play a role. Acute inflammation and necrosis involving capillaries, arterioles, and small muscular arteries has been described [20]. The involvement of capillaries is manifested by an infiltrate of necrotic neutrophils within alveolar septa often associated with destruction of the alveolar wall. This capillaritis was present in all four cases originally described by Myers and Katzenstein [20], while involvement of arterioles and small arteries was seen in three. Immunofluorescence and electron microscopy demonstrated immune complexes in only two. In a recent series of 90 necropsies in patient s with SLE, capillaritis was observed in 3 of 23 patients with alveolar hemorrhage [21]. Capillaritis is not specific of SLE since it has also been described in alveolar hemorrhage associated with the antiphospholipid syndrome, in polymyositis and other connective tissue diseases, in Henoch-Schoenlein purpura, cryoglobulinemia, Behçet syndrome, and Wegener disease [22–24]. It may also be seen in antibasement membrane antibody disease.

Diffuse alveolar hemorrhage reveals SLE in 11–20 % of the cases [16]. Patients with lupus nephritis are at increased risk of developing alveolar hemorrhage, and renal involvement is observed in 60–93 % of the patients at diagnosis of diffuse alveolar hemorrhage. Microvascular renal and lung involvement appear to be pathogenetically similar [25]. The presentation ranges from asymptomatic to fulminant. Affected patients are young (mean age: 27 years) and present acutely ill with dyspnea, cough, fever and recent drop of hemoglobin blood levels [26]. Symptoms are usually abrupt in onset, being present for less than 3 days in two thirds of patients. Hemoptysis is initially present in less than half of patients. Bilateral lung infiltrates, ranging from limited ground glass opacities (Fig. 26.2) to dense consolidations are present. Arterial hypoxemia is common and more than 50 % of the patients will need mechanical ventilation [16].

The diagnosis of alveolar hemorrhage is usually easily obtained with bronchoalveolar lavage, which allows for a search for infectious agents. Concomitant lung infection, bacterial, fungal or viral, is observed in about one third of patients, and bears a poor prognosis [16]. Lung biopsy, either transbronchial or surgical, is not useful once the diagnosis of SLE is ascertained with the presence of antinuclear antibodies, and may be dangerous in critically ill patients. Echocardiography is mandatory to evaluate the presence of valvular or myocardial dysfunction. The classical increase of DLCO observed at the early stages of alveolar hemorrhage is of limited interest in critically ill patients [27].

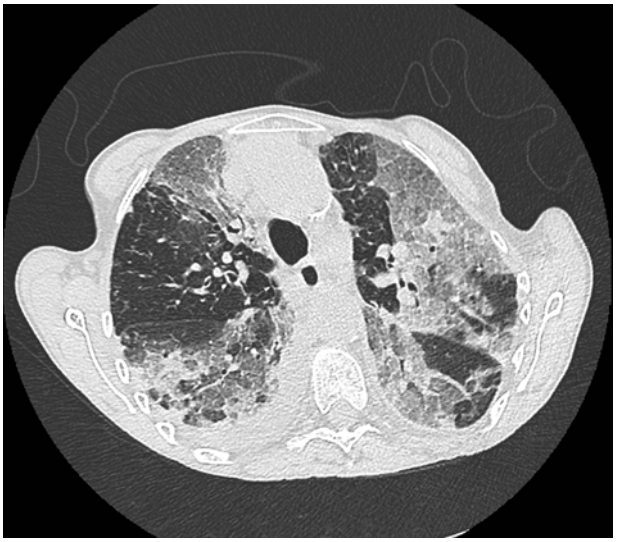

Fig. 26.2 Catastrophic antiphospholipid syndrome in a woman with longstanding systemic lupus erythematosus and antiphospholipid syndrome. No trigger was identified. CT scan shows multiple well limited ground glass opacities with some areas of consolidation, with a right pleural effusion. Bronchoalveolar lavage fluid analysis showed a neutrophilic alveolitis. Partial improvement was obtained with corticosteroids

The treatment of SLE-associated alveolar hemorrhage is not well defined. High dose corticosteroids are commonly used (methylprednisolone 1 g daily for 3 days, progressively decreased over the next days) but corticosteroids alone does not appear to be very effective. In a recent series, diffuse alveolar hemorrhage developed in patients already treated with high dose corticosteroids for lupus nephritis [17]. A combination of corticosteroids, cyclophosphamide and plasmapheresis has been used with promising results [28, 29]. Plasmapheresis should be reserved for patients with severe alveolar hemorrhage refractory to corticosteroids and cyclophosphamide [30]. A systematic search of respiratory infections and the addition of broad-spectrum antibiotics for the initial treatment of lupus patients with diffuse alveolar hemorrhage is recommended based on the lower mortality reported in some studies [19, 31]. Survivors are exposed to the risk of developing pulmonary fibrosis [32]. Diffuse alveolar hemorrhage may recur several times in the same patient but the factors associated with recurrence are not well understood. In a recent series from Mexico, an increased risk of death was associated with thrombocytopenia, renal failure, requirement for mechanical ventilation and high severity

score as assessed by the Acute Physiology And Chronic Health Evaluation II score (APACHE II) [33].

Acute Respiratory Distress Syndrome

The prevalence of adult respiratory distress syndrome (ARDS) ranges from 3.5 to 15 % of patients with lupus [34]. A retrospective study of 544 Korean lupus patients found 19 (3.5 %) cases of ARDS with a mortality rate of about 70 % [34]. Death related to ARDS was found in one third of all deaths from lupus during the 4-year study period. The most frequent cause of ARDS was sepsis or bacteraemia (47.4 %). The main organisms causing the sepsis were gram-negative bacilli (61.5 %). The ARDS developed at a younger age and progressed more rapidly than ARDS in non-SLE patients.

Catastrophic Antiphospholipid Syndrome

The catastrophic antiphospholipid syndrome is a rare and excessively severe manifestation of the antiphospholipid syndrome which is observed both in primary and secondary antiphospholipid syndrome [35] (Fig. 26.2). The syndrome is characterized by multiple simultaneous vascular occlusions throughout the body. The lung is involved in 66 % of the cases, with ARDS, pulmonary embolism, pulmonary artery thrombosis, pulmonary microthrombi, or alveolar hemorrhage, sometimes associated [36]. About 50 % of the patients die with the syndrome. Lung involvement and presence of SLE is associated with a twofold increased risk of death [37]. With an adequate treatment, including high dose steroids, anticoagulation, plasma exchanges or intravenous immunoglobulins, the prognosis seems better, and a mortality below 10 % is observed in experienced groups [38]. Long term anticoagulation is needed after recovery, as well as the treatment of SLE.

Chronic Interstitial Lung Disease

Clinically significant chronic interstitial pneumonia rarely complicates SLE and extensive lung fibrosis is rarely observed (3 % of the patients in one study) (Figs. 26.3 and 26.4) [39]. An autopsy study of 120 patients with lupus revealed a prevalence of interstitial pneumonitis or fibrosis of about 13 % [8]. However systematic CT evaluation of non selected patients with SLE demonstrated the high prevalence of subclinical interstitial abnormalities, observed in 30–40 % of the patients [40]. Detected abnormalities consist mainly of thickened inter-lobular walls, of limited extension, and usually predominant in the subpleural regions. Pulmonary function tests were abnormal in about 50 % of the patients with

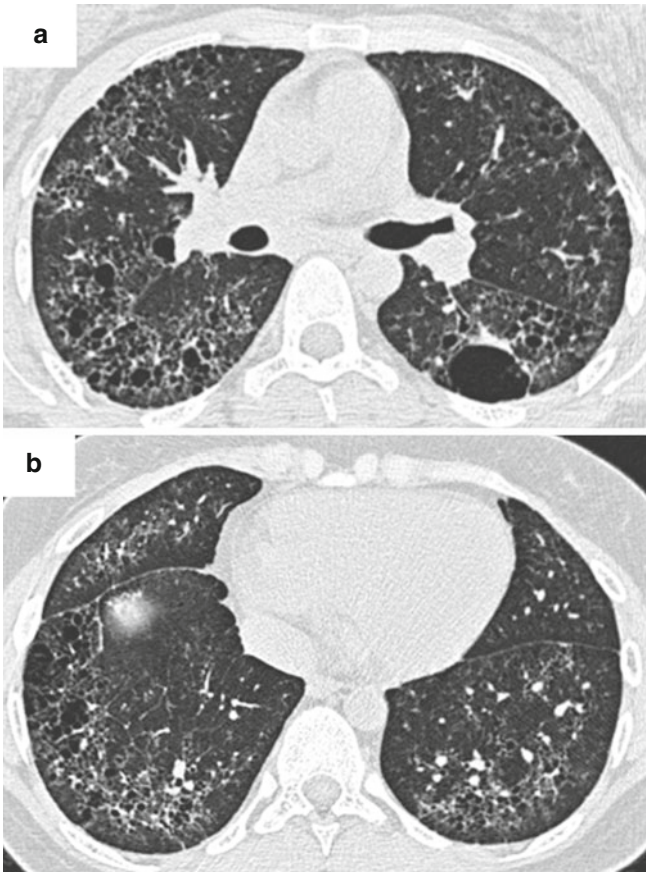

Fig. 26.3 (**a**, **b**) Lung fibrosis in a patient with systemic lupus erythematosus. Cysts of different size are observed, associated with reticulations

abnormal HRCT, but HRCT changes did not correlate with pulmonary function abnormalities [40]. In one series, however, the extent of disease was statistically significantly correlated with duration of clinical history and decreased single-breath diffusing capacity for carbon monoxide and ratio of forced expiratory volume in 1 s to forced vital capacity [40].

The larger series of Eisenberg and colleagues described 18 patients, identified over a 1-year period, with radiographic evidence of pulmonary fibrosis, representing less than 3 % of the patients followed at their institution [39]. All the patients had a restrictive functional pattern but only seven were symptomatic. In most cases, chronic ILD develops insidiously, sometimes with mild flares of lung involvement [39]. In some patients, lung fibrosis could be the sequela of acute pneumonitis. Lung involvement does not correlate with any biological characteristic, although an association between anti-SS-A antibodies or anti-U1 RNP antibodies and chronic interstitial pneumonia was observed [41, 42].

Histologic reports describe non specific abnormalities with interstitial lymphocytic infiltrates, interstitial fibrosis, and honeycomb changes, sometimes associated with follicular bronchiolitis [39, 43]. Non specific interstitial pneumonia

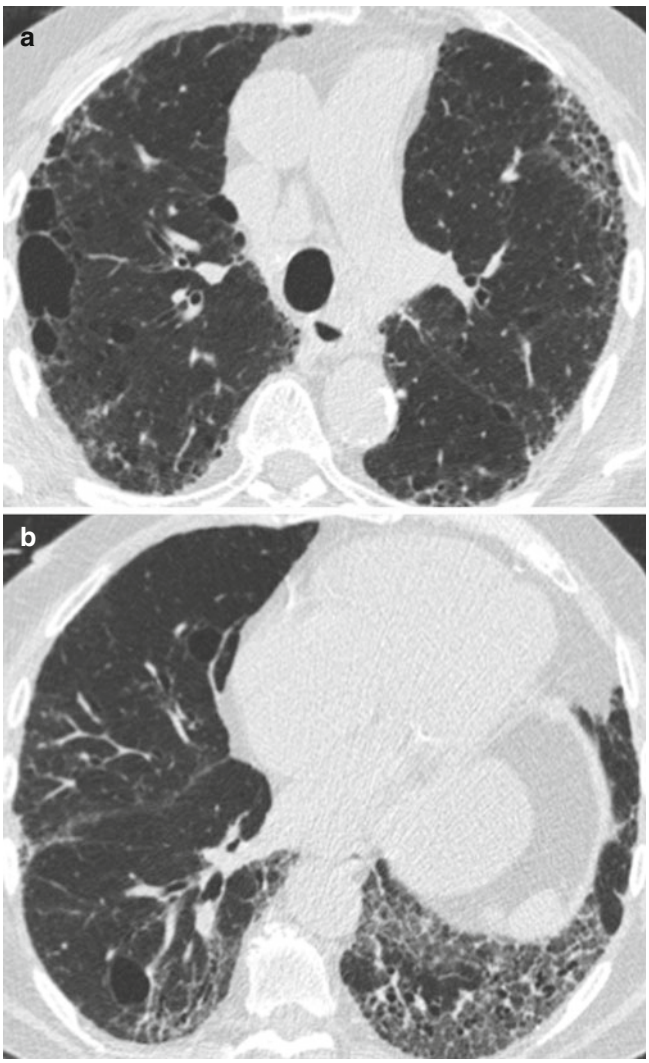

Fig. 26.4 (**a**, **b**) Combined pulmonary fibrosis and emphysema syndrome in a patient with systemic lupus erythematosus

(NSIP) is likely the most common pattern in patients with pulmonary fibrosis, although the real incidence of NSIP in SLE is still not well defined. Desquamative interstitial pneumonia has been reported [44]. Long term evolution of chronic ILD in SLE is poorly known and treatment is not evaluated. In the Weinrib's series, all patients were treated with corticosteroids, and the condition improved in 9/14 [39]. Improvement with oral methotrexate, mycophenolate mofetil or UVA has been reported [45].

Lymphocytic interstitial pneumonia (LIP) has been described in a few patients with SLE, usually in association with Sjögren's syndrome [46, 47]. In these cases, the development of lung cysts should suggest the diagnosis of LIP [47]. Finally, the clinicoradiologic syndrome of organizing pneumonia (formerly known as BOOP) characterized by patchy alveolar infiltrates and an histologic pattern of organizing pneumonia has been described in patients with SLE (Fig. 26.5). These cases usually demonstrate a rapid improvement with corticosteroids [48]. The concurrence of sarcoidosis and SLE has been reported in a few cases [49]. Nodular amyloidosis, excavating nodules, have also been observed.

The Shrinking Lung Syndrome

The term "shrinking lung syndrome" has been applied to SLE patients presenting with progressive dyspnea, the characteristic chest radiographic findings of small lung volumes, elevated hemidiaphragms and bibasilar infiltrates, with a restrictive ventilatory defect and a preserved carbon monoxide transfer coefficient [50] (Fig. 26.6). Pleuritic pain is also a frequent symptom in these patients [51]. Shrinking lung syndrome can be present in any phase of the disease and can even be its first manifestation. This syndrome was attributed to diaphragmatic dysfunction on the basis of the demonstration of decreased inspiratory muscle strength in 11 SLE patients [52]. Conversely, Laroche et al., using bilateral electrostimulation in 12 patients with the shrinking lung syndrome, failed to demonstrate diaphragm weakness [53]. In a well documented case, Hardy described a patient with the syndrome and bilateral phrenic nerve paralysis [54]. With corticosteroids, the phrenic nerve function recovered whereas the restrictive functional pattern persisted, suggesting that reduced diaphragm muscle contractility per se does not explain the small volume lungs and respiratory symptoms in patients with the syndrome. Hawkins reached similar conclusions in a different patient [55]. However, lupus myopathy has been associated with the syndrome [56]. We suggest that recognition of this syndrome requires a thorough evaluation to determine its cause and give the adequate treatment.

Some improvement of dyspnea and restriction has been observed with corticosteroids [50, 57]. Anecdotal data support the use of theophyllin, beta-2-agonists, cyclophosphamide, azathioprine, or rituximab, in patients unresponsive to steroids [58, 59]. Patients seem to stabilize and have no worsening of lung function with time.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the most common connective tissue disease (see Table 26.2 for classification criteria). As is the case for SLE, the pleuropulmonary manifestations of RA are varied, pleural abnormalities and ILD being the more common. Although RA affects women preferentially, men are more affected by pleuropulmonary manifestations of the disease. The diagnosis of RA is helped by serological markers, rheumatoid factor and anti-

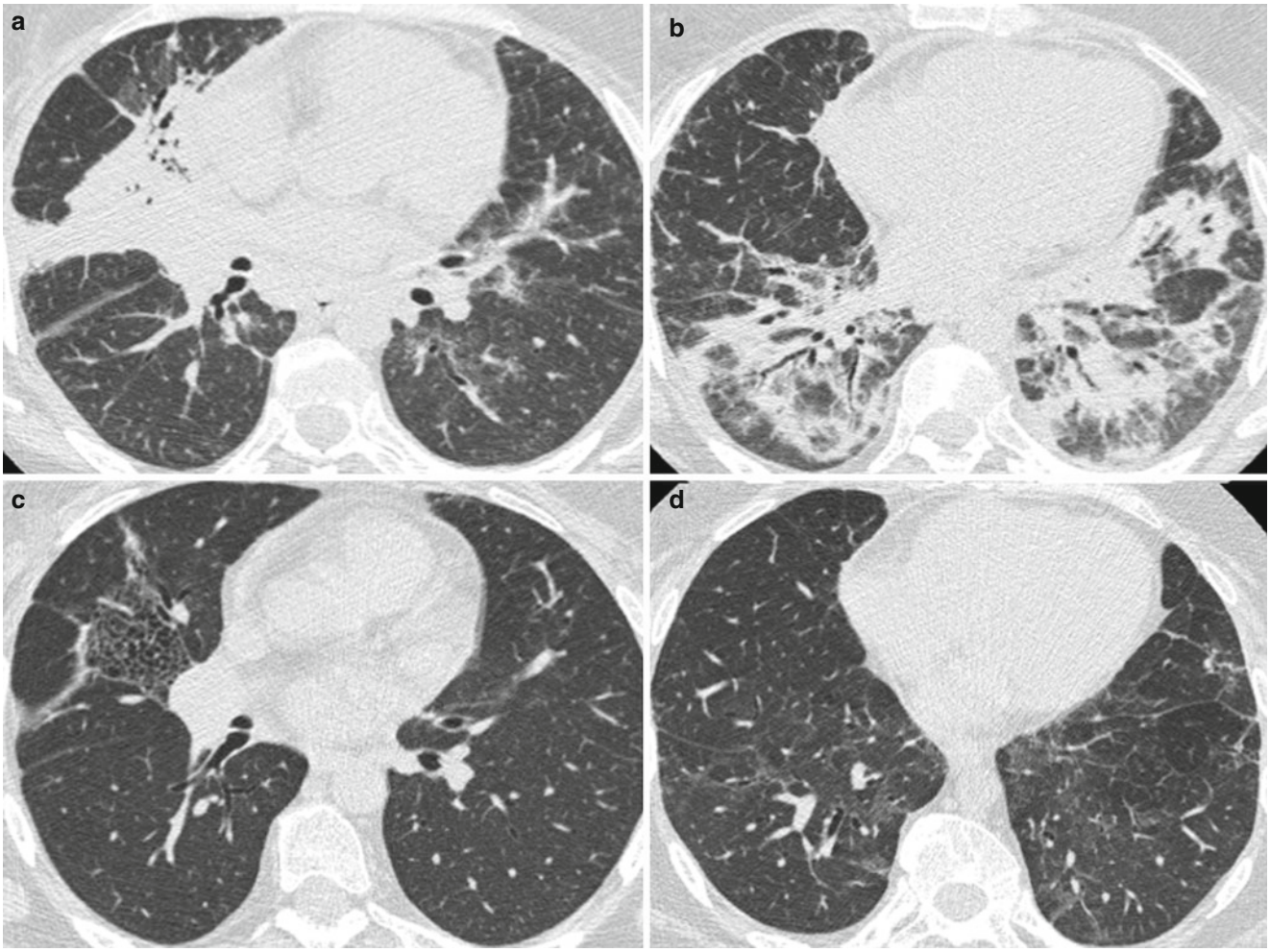

Fig. 26.5 Organizing pneumonia revealing systemic lupus erythematosus. Bilateral consolidations (panels **a**, **b**) resoved with corticosteroids (panels **c**, **d**)

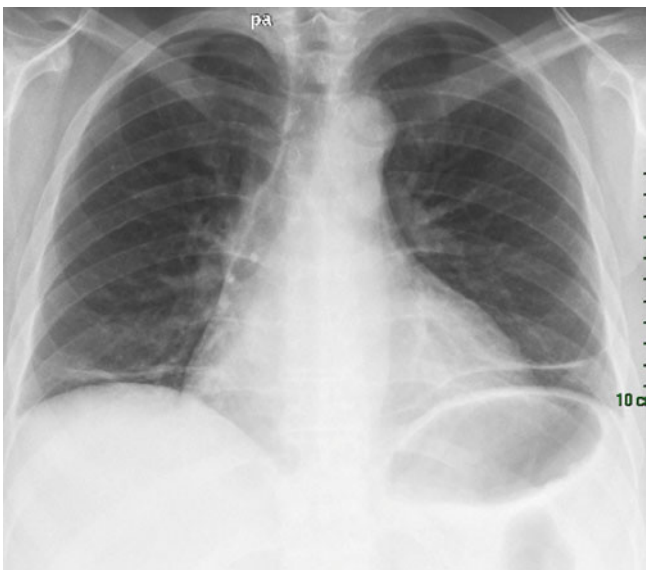

Fig. 26.6 Shrinking lung syndrome in a patient with systemic lupus erythematosus. Note the rise of diaphragm and the linear basal opacities

cyclic citrullinated peptide antibodies which are included in the 2010 rheumatoid arthritis classification criteria [60]. Tobacco-smoking is a risk factor for the development of ILD in patients with RA and is a strongly associated environmental risk factor for RA. There is a strong association between cigarette smoking and the presence and titre of rheumatoid factors [61, 62]. Although not replicated in all cohorts, recent studies demonstrate that the increased risk conferred by tobacco exposure is restricted to the anti-cyclic citrullinated peptide antibodies -positive subset of subjects and is associated with HLA-DR alleles [63, 64]. Analysis of lung samples from smokers shows citrullination of cellular proteins that is not present in nonsmoking subjects thereby providing a source of citrullinated antigens to induce autoantibody production [65]. There is evidence of RA-specific antibodies in patients wit ILD without RA [66]. The level of anti-cyclic citrullinated peptide antibodies are increased in patients with RA with exposure to tobacco [67].

Table 26.2 American College of Rheumatology/European League against Rheumatism Classification criteria for Rheumatoid arthritis [200]

The criteria apply to patients with at least one clinical synovitis not better explained by another diagnosis.
Score of ≥6 points:
1. Joint involvement
(a) 1 large joint (0 points)
(b) 2–10 large joints (1 point)
(c) 1–3 small joints (2 points)
(d) 4–10 small joints (3 points)
(e) More than 10 joints (at least one small) (5 points)
2. Serology
(a) Negative rheumatoid factor (RF) and negative anticyclic citrullinated peptide antibody (aCCP) (0 points)
(b) Low positive RF or aCCP (≤3 times the upper limit of normal (2 points)
(c) High positive RF or aCCP (>3 times the upper limit of normal (3 points)
3. Acute phase reactants
(a) Normal C-reactive protein and normal erythrocyte sedimentation rate (0 points)
(b) Abnormal C-reactive protein or abnormal erythrocyte sedimentation rate (1 point)
4. Duration of symptoms
(a) <6 weeks (0 points)
(b) ≥6 weeks (1 point)

Frequency of Interstitial Lung Disease

Interstitial lung disease is the predominant pulmonary manifestation of RA. ILD is usually detected in patients already diagnosed with RA (mostly between the ages of 50 and 60 year), but isolated pulmonary disease may precede the onset of articular disease [68]. Clinically significant RA-ILD affects 7–10 % of patients with RA [68–70], whereas a higher prevalence was found by autopsy studies (interstitial changes are observed in 80 % of lung biopsies) or prospective screening studies using high-resolution chest tomography (up to 50 %) or lung function tests (a decrease of the diffusing capacity of carbon monoxide is observed in up to 40 % of RA patients) [71, 72]. In a population-based incidence cohort of patients with RA and a matched cohort of individuals without RA, the hazard ratio (HR) of developing ILD in RA patients was 8.96 (95 % confidence interval [95 % CI] 4.02–19.94) as compared with controls [68]. The risk of developing ILD was higher in RA patients who were older at the time of disease onset, in male patients, and in individuals with more severe RA [68]. The risk of death for RA patients with ILD was three times higher than in RA patients without ILD (HR 2.86 [95 % CI 1.98–4.12]). Median survival after ILD diagnosis was only 2.6 years. In that study, ILD contributed approximately 13 % to the excess mortality of RA patients when compared with the general population. Whereas overall mortality rates for RA have fallen, those associated with RA-ILD have increased significantly in older age groups [70]. The presence of ILD was associated with a reduction of life expectancy of about 2 years [70, 73]. Asymptomatic preclinical ILD, which is detectable by HRCT, may be prevalent (up to 35 % of patients without respiratory symptoms) and progressive (in about half the patients in one series) among patients having RA [74–76]. Cigarette smoking seems to be associated with preclinical ILD in patients having RA, and treatment using methotrexate may be a risk factor for progression of preclinical ILD [75]. The influence of disease-modifying antirhumatic drugs on the development and evolution of RA-ILD is unknown. Recent data from the British data base suggest that the mortality associated with RA-ILD is not increased by antiTNF agents [77].

Histopathological Patterns

Histopathological findings in RA-associated ILD disclose very different patterns, sometimes associated : Usual interstitial pneumonia (UIP), NSIP, Desquamative interstitial pneumonia, LIP, organizing pneumonia, eosinophilic infiltration [9]. Many cases are difficult to classify into one pattern. Follicular bronchiolitis consisting of lymphoid hyperplasia and reactive germinal centers along small airways is also detected, associated or not with a LIP pattern [78]. The relative prevalence of each histopathological pattern varies according to the studies, however the currently available data indicate that the histopathological pattern of UIP may be equally as frequent as NSIP in patients with RA-ILD, contrasting with the predominance of NSIP in the other connective tissue diseases [79]. However, UIP in connective tissue disease may not exactly replicate idiopathic UIP (as in idiopathic pulmonary fibrosis), with fewer fibroblastic foci [80, 81], smaller honeycombing spaces, and more pronounced inflammation and germinal centres [81]. A trend was found toward worse survival of RA-ILD with UIP histological pattern as compared to those with a NSIP pattern [82].

Radiographical Patterns

The most common CT features of RA-ILD are ground glass opacities (90 % of patients) and reticulations (98 % of patients) [83]. In that study, four major CT patterns were identified: UIP (n = 26) (Fig. 26.7), NSIP (n = 19) (Fig. 26.8), bronchiolitis (n = 11), and organizing pneumonia (n = 5). There was a good concordance between the HRCT pattern and the histopathological pattern [83].

The prognosis of RA-associated ILD is usually good as the deterioration of lung function is slow [74, 75]. However one study reported a median survival of 3.5 years and a 5-year survival rate of 39 % in 49 patients with RA hospitalized for interstitial pulmonary fibrosis, a survival very similar to what is observed in patients with idiopathic

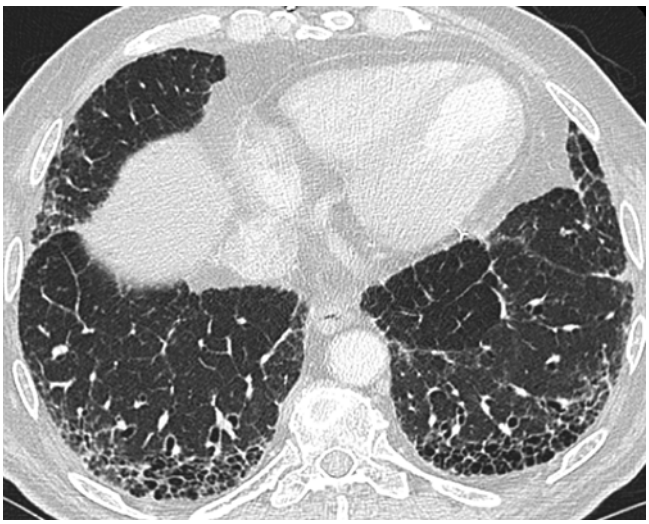

Fig. 26.7 A usual interstitial pneumonia (UIP) pattern in a patient with rheumatoid arthritis

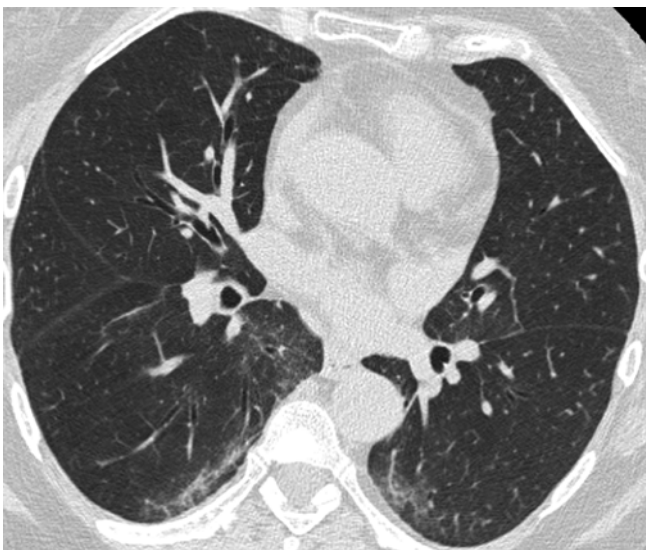

Fig. 26.8 A non specific interstitial pneumonia (NSIP) pattern in a patient with rheumatoid arthritis

pulmonary fibrosis [84]. The prognosis of RA-ILD is better assessed by the HRCT pattern. In a recent study based on HRCT, a definite UIP pattern was seen in 20 (24 %) out of 82 patients with RA-ILD. These patients showed worse survival than those without this pattern (median survival 3.2 versus 6.6 years), and a similar survival to those with idiopathic pulmonary fibrosis [85]. On multivariate analysis, a definite UIP pattern on HRCT was associated with worse survival (hazard ratio of 2.3). Analysis of specific HRCT features demonstrated that traction bronchiectasis and honeycomb fibrosis were associated with worse survival (hazard ratio of 2.6 and 2.1, respectively). Female sex (hazard ratio of 0.30) and a higher baseline diffusing capacity of the lung for carbon monoxide (hazard ratio of 0.96) were associated with better survival [85]. This was confirmed by Tsuchiya and colleagues who observed that the 5-years survival rates were 36.6 % in the UIP group and 93.8 % in the NSIP group [86]. These studies suggest that a pragmatic imaging-based approach is possible and routinely applicable to approach the prognosis in RA-associated ILD [87], although the case of patients with undefinite HRCT pattern remains uncertain [85].

Treatment of RA-ILD

Treatment of RA-ILD is not well defined. It should be tailored according to the pattern of lung involvement. If organizing pneumonia or NSIP patterns predominate, with ground glass and consolidations, corticosteroids are first-line therapy and may be effective alone, but most often an immunosuppressant will be needed. If the HRCT pattern is uncertain, a combination of steroids and immunosuppressants may be used, over a limited period of time and maintained if an objective improvement of lung function tests is obtained. In case of a UIP pattern, some still consider a combination of steroids and immunosuppressants [88]. Cyclophosphamide, azathioprine, methotrexate, cyclosporine, have been used. At this time, the best treatment regimen is not defined. Improvement of lung involvement has been reported in one case with blockade of interleukin-6 receptor [89].

Acute Exacerbation of RA-ILD

An ILD exacerbation is generally defined as rapidly deteriorating respiratory symptoms within a 30-day period with evidence of new infiltrates (usually new ground glass opacities) and exclusion of an identifiable cause. The absolute risk of an acute exacerbation is not well established, but based on the limited data of acute exacerbations in collagen vascular diseases, possibly as many as 20 % of patients with RA-ILD will experience an acute exacerbation with a 1-year incidence as high as 2.58 % [90]. By the time patients present to the hospital, hypoxemia may be severe and a ventilatory support may be needed.

The diagnosis of exacerbation requires the exclusion of alternative explanations for a clinical worsening, such as infection, drug reaction, left ventricular failure or pulmonary embolism. Treatment usually associates methylprednisolone pulses and immunosuppressants (IV cyclophosphamide) [90, 91]. The prognosis is very poor [90, 91].

Rheumatoid Nodules

Rheumatoid nodules are the only specific lesion observed in the lung of RA patients. Rheumatoid nodules are

histologically similar to that observed in the subcutaneous tissue. Occasionally, giant cells and well-formed granulomas may be observed in the peripheral region of the nodule [72]. Very frequent at microscopic examination of the lung (30 %), or on HRCT lung slices (20 %), nodules are seldom seen on standard chest X ray (<1 %). Nodules usually predominate in the upper and mid-lung regions, in the peripheral sub-pleural zone, although endobronchial nodules do exist. The nodules are more prevalent in smokers, in males, and in patients with extra-articular manifestations or with subcutaneous nodules [92]. Multiple widespread nodules have been described as rheumatoid nodulosis and may be induced by treatment such as methotrexate, leflunomide or antiTNF agents [93–95]. Nodules are usually asymptomatic and do not evolve over time, but cavitation and infection may occur [96]. Detection of one or more lung nodules in a patient with RA poses the problem of their nature. A systematic diagnostic workup is needed in order not to miss an infectious or tumoral lesion. Increased fluorine-18-fluorodeoxyglucose uptake may be misleading [97].

A syndrome of bilateral lung nodules in silica-exposed RA patients has been described as the Caplan's syndrome, also observed in other dust exposed RA patients [98]. The histopathological image of the nodules is similar to the rheumatoid nodule except for the presence of an additional peripheral pigmented dust surrounding the lesion [72]. Most patients have a pre-existing mild pneumoconiosis.

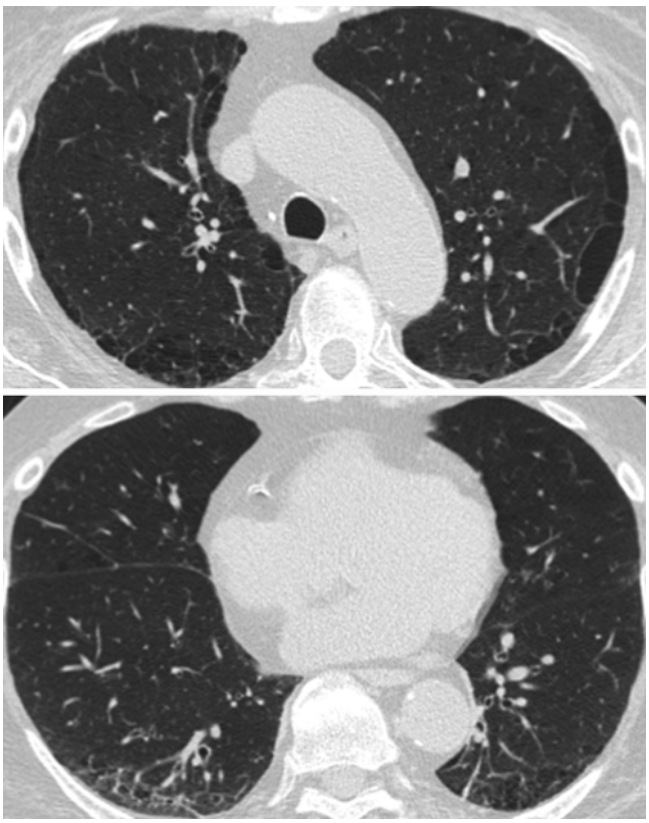

Fig. 26.9 Combined pulmonary fibrosis and emphysema syndrome in a patient with rheumatoid arthritis. Paraseptal emphysema is observed in the upperlobes (*upper panel*) while subpleural reticular opacities are evident in the lower lobes (*lower panel*)

Other Patterns

Combined pulmonary fibrosis and emphysema was described in 18 RA patients [99] (Fig. 26.9). Patients with combined pulmonary fibrosis and emphysema had higher lung volumes, lower diffusion capacity, higher pulmonary artery pressures, and more frequently were male than those with connective tissue diseases and lung fibrosis without emphysema [99]. Secondary amyloidosis involving the lung with an interstitial pattern is a rare but possible complication of long lasting RA [100]. Apical fibrobullous disease, similar to what is observed in patients with ankylosing spondylarthritis, is observed in RA patients [101].

Alveolar haemorrhage related to pulmonary vasculitis has been reported [102], sometimes with antineutrophil cytoplasmic antibodies [103] (Fig. 26.10).

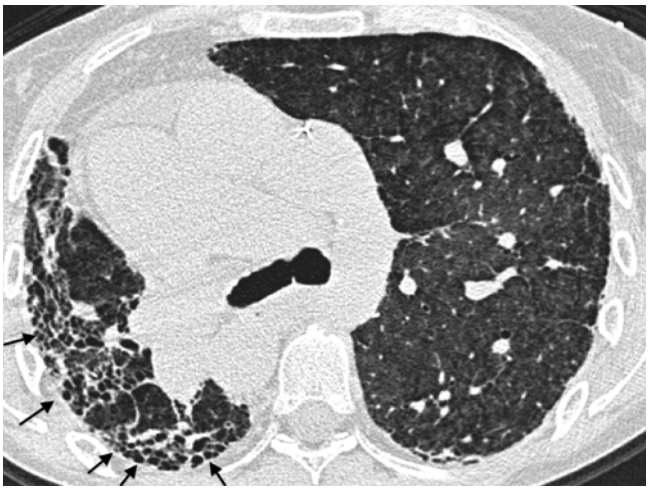

Fig. 26.10 A woman with rheumatoid arthritis and lung fibrosis with a right lung predominance (typical honeycombing with loss of volume is present in the right lung) developed an acute alveolar hemorrhage with diffuse ground glass opacities in the left lung. ANCA-associated vasculitis involving the lung and the kidney was diagnosed. *Arrows*: typical honeycombing in the right lung

Drug-Induced Lung Disease

Almost all drugs used for the treatment of RA have been associated with drug-induced lung disease. Undesirable respiratory side-effects of methotrexate, gold salts, D-Penicillamine, and nonsteroidal anti-inflammatory drugs are very well described. However, new compounds (such as anti-TNF agents, sirolimus, leflunomide, tocilizumab, rituximab), and new clinicoradiological patterns are continuously described [77, 104–107]. Reference to available comprehen-

sive reviews [108] and to Pneumotox®, an internet searchable database which gives up-to-date information for this rapidly evolving field are needed in order to determine whether any respiratory abnormality in a RA patient could be secondary to the treatment received. There could be a genetic predisposition to drug-induced pneumonitis [109], as suggested by the observation that the incidence of leflunomide-associated pneumonitis is 0.1 % in western populations and 1 % in Asian populations [110, 111]. Interestingly, a preexisting ILD increases the risk of developing a drug-induced pneumonia, as shown with methotrexate, leflunomide or anti-TNF molecules [106, 110–112]. For instance, a preexisting ILD increases 7-fold the risk of methotrexate-associated pneumonitis [112], and eightfold the risk of leflunomide-associated pneumonitis [111]. This suggests that the lung is primed to inflammatory reaction in patients with RA.

A preexisting ILD is usually not a contraindication to the use of MTX, leflunomide or anti-TNF agents in patients with rheumatoid arthritis, since these drugs are very useful for the patients, and the basal risk of pneumonia development in a given patient remains very low, even in case of preexisting ILD. However, the respiratory consequences of a drug-induced pneumonitis will be worst in case of preexisting ILD and mortality associated with drug-induced ILD is increased twofold in patients with underlying ILD [106]. Some experts recommend that patients with RA starting methotrexate undergo a baseline chest radiograph and pulmonary function tests, which can be used for comparison if respiratory symptoms develop [113], although this has not been incorporated into formal guidelines. The 2008 recommendations on RA treatment issued by the American College of Rheumatology stated that methotrexate was contraindicated in the presence of clinically important RA-associated pneumonitis or interstitial lung disease of unknown cause [114]. This recommendation was not amended in the 2012 updated recommendations [115]. No definition of a clinically important ILD was given in that recommendation, but we may suggest that methotrexate should be avoided in a patient with RA-associated ILD responsible for chronic respiratory insufficiency requiring oxygen therapy. If methotrexate use is deemed hazardous, one may consider using preferentially rituximab (anti-CD20) since the lung-toxicity of this drug was essentially described outside of the rheumatology field [107, 116], instead of leflunomide or anti-TNF agents.

Sjögren's Syndrome

The Sjögren's syndrome (SS) is one of the most common autoimmune diseases, characterized by the infiltration of different organs by CD4-positive T lymphocytes, the lacrymal and salivary glands being the most often involved (see Table 26.3 for classification criteria). The classic triad associates xerostomia (dry mouth), xerophtalmia (dry eyes) and arthritis. Multiple diagnosis criteria have been proposed, and have been recently updated [117]. Criteria now require the presence of either an anti-SSA or anti-SSB autoantibody, or a typical lesion on the accessory gland biopsy (Chisholm grade 3 or 4). Detection of an anti-SSA antibody in a patient with idiopathic ILD is rarely indicative of a SS [118]. SS may be isolated (primary SS) or associated with a definite connective tissue disease (secondary SS, primarily with RA). These criteria have a specificity of 97 % and a sensitivity of 90 % for the diagnosis of secondary SS. Lung involvement is less common and less severe in primary SS than in secondary SS.

Table 26.3 Classification criteria for Sjögren's syndrome

SICCA (Sjögren's International Collaborative Clinical Alliance Cohort) 2012 criteria [201]
At least 2 of the following 3 objective features: 1. Positive serum anti-SSA/Ro and/or anti-SSB/La or (positive rheumatoid factor and ANA titer ≥1:320) 2. Labial salivary gland biopsy exhibiting focal lymphocytic sialadenitis with a focus score ≥1 focus/4 mm^2 (Chisholm grade ≥3) [202] 3. Keratoconjunctivitis sicca with ocular staining score ≥3 (assuming that individual is not currently using daily eye drops for glaucoma and has not had corneal surgery or cosmetic eyelid surgery in the last 5 years) [203]
Prior diagnosis of any of the following conditions would exclude participation in SS studies or therapeutic trials because of overlapping clinical features or interference with criteria tests: History of head and neck radiation treatment; Hepatitis C infection; acquired immunodeficiency syndrome; sarcoidosis; amyloidosis; graft versus host disease; IgG4-related disease

Prevalence of Interstitial Lung Disease

The reported prevalence of pulmonary disease in SS varies widely according to the diagnostic modalities used to identify the abnormalities. HRCT detects abnormalities in 34–65 % of SS patients evaluated [119–123]. A comprehensive evaluation including lung function tests detected abnormalities in 75 % of SS patients [124]. However, if one considers only clinically significant pulmonary disease, it is estimated to affect less than 10 % of SS patients although a 22 % prevalence has been recently reported [125, 126]. Airways involvement and ILD are the most frequent manifestations of lung involvement in SS.

Interstitial lung disease is common in patients with SS and may reveal the disease. It affects 8–38 % of patients with primary SS. Bronchoalveolar lavage has demonstrated the high prevalence of subclinical lymphocytic and neutrophilic alveolitis, affecting 50 % of SS patients [127]. Alveolitis is more frequent in patients with extra-pulmonary involvement. An expansion of CD8+ T-lymphocytes has been associated with more frequent alteration of lung function tests [128].

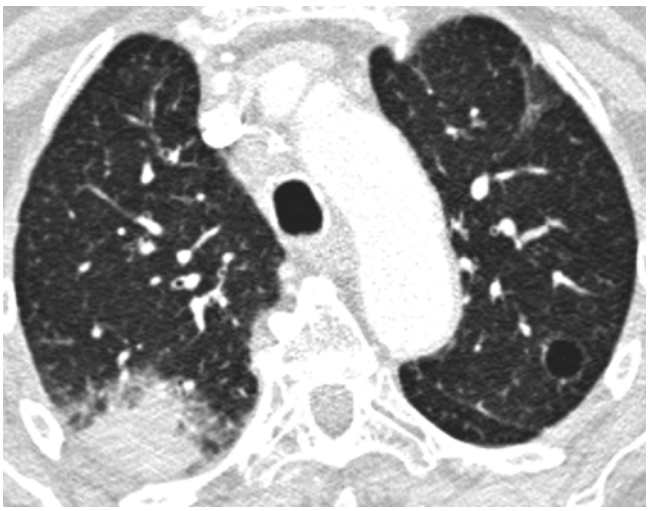

Fig. 26.11 Acute organizing pneumonia in a woman with a primary Sjögren's syndrome. Note the cyst of the upper left lobe

Histopathology

The histopathology of ILD in SS is not specific. Different histological patterns may be observed, sometimes associated in a given individual: desquamative interstitial pneumonia, NSIP, UIP, LIP, organizing pneumonia, end stage lung [9, 129–131]. Bronchiolitis is frequently associated. NSIP is the more common pattern [130, 131]. Well formed granulomas may be seen in up to 10 % of samples [129].

Clinical Patterns

As in other connective tissue diseases, various radioclinical presentations are possible, and can be classified according to the chronology of involvement.

- Acute or subacute infiltrating pneumonia, developing over several days or a few weeks may be due to organizing pneumonia [132] (Fig. 26.11), acute NSIP, eosinophilic pneumonia [133] or sometimes an exacerbation of a previously unrecognized diffuse infiltrative pneumonia [134]. This may be the first presentation of Sjögren's syndrome. In this setting, alveolar haemorrhage is very rare and requires the search for cryoglobulinaemia [135] or an associated connective tissue disease, mainly systemic lupus erythematosus. Organizing pneumonia in the context of SS respond quite well to corticosteroids.
- Chronic ILD, developing over several weeks or several months.

This type of involvement can reveal SS. The radiographic appearance can suggest NSIP with ground glass opacities, mainly subpleural and posterior, with signs of fibrosis variable in extent (subpleural reticulations, sometimes honeycomb cysts) (Fig. 26.12). Disease progression is often very slow, over many years. It is often difficult to

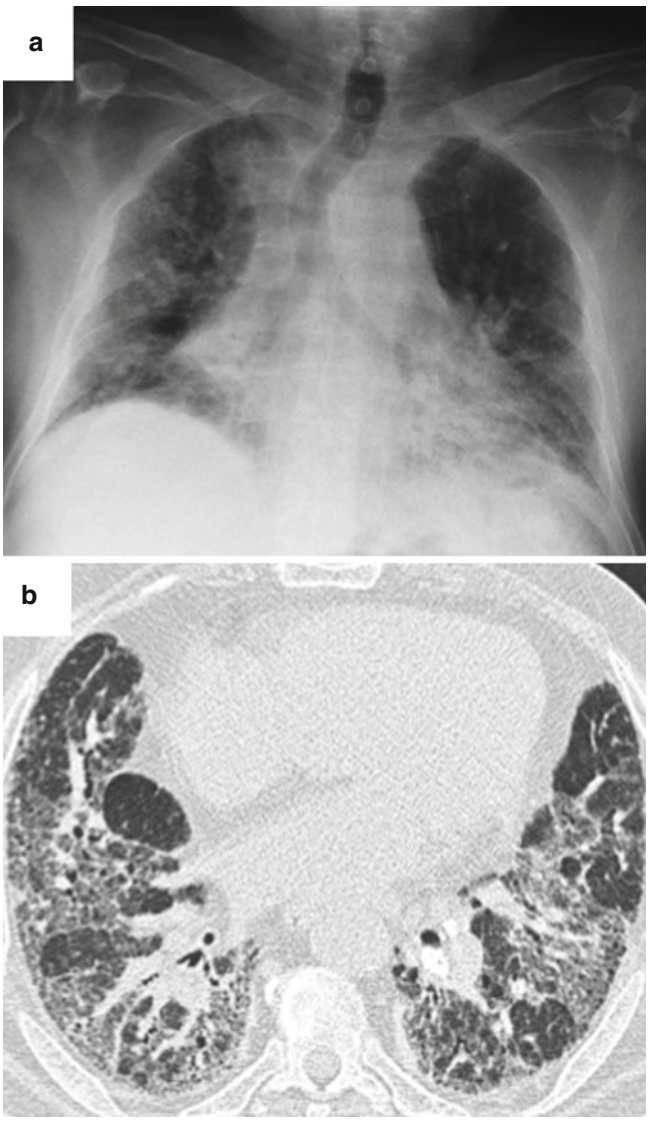

Fig. 26.12 Lung fibrosis with a fibrotic NSIP pattern revealed the primary Sjögren's syndrome. Chest X ray (panel **a**) and CT scan (panel **b**)

differentiate from LIP in the absence of a surgical lung biopsy. In some cases, imaging is suggestive of UIP with honeycomb cysts peripheral and subpleural in distribution (Fig. 26.13).

Information concerning the evolution and the treatment of ILD in SS are limited. Available data suggest that ILD in primary SS has a good prognosis without evidence of clinically significant deterioration over time in most patients [125, 136–138], although progression of lung disease with development of chronic respiratory failure may occur, particularly in patients with a UIP pattern [138]. In a recent series, 5 years survival rate of patients with SS and ILD was 84 % [137]. Ten of thirty-three patients died in the course of the follow-up period: five with fibrosing NSIP, two with malignant lymphoma, one with chronic bronchiolitis, two with fibrosis. Nine of the ten patients died of causes related

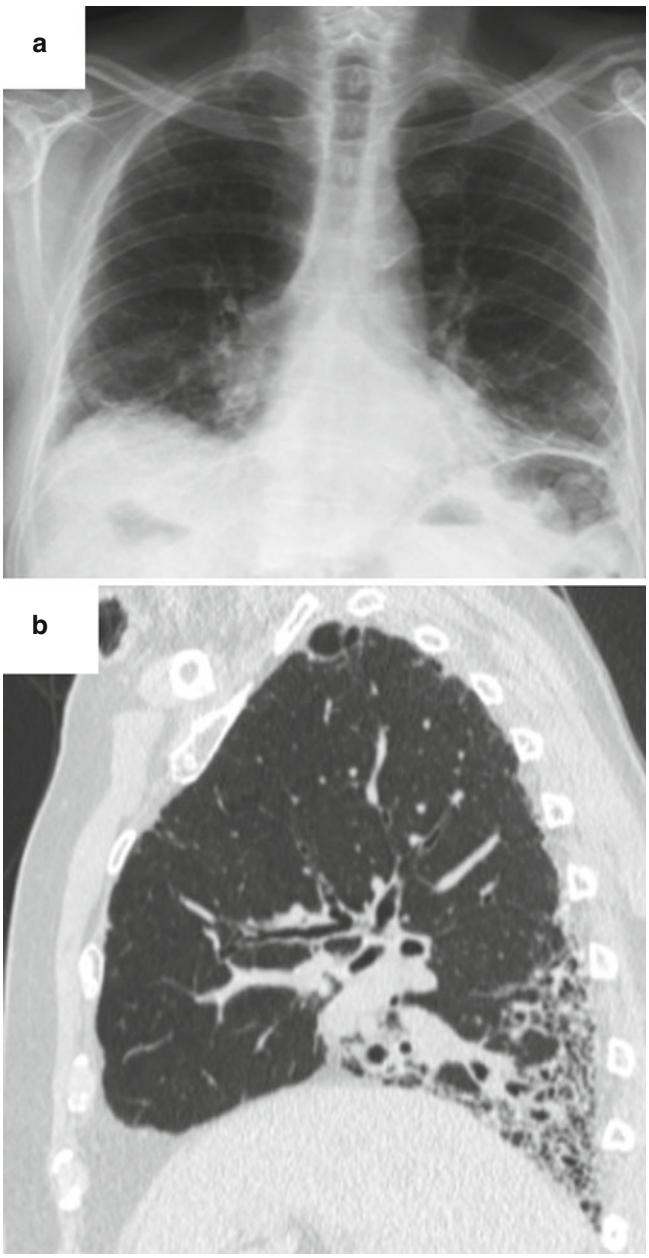

Fig. 26.13 Lung fibrosis with UIP pattern in a patient with primary Sjögren's syndrome. Chest X ray (panel **a**) and CT scan (panel **b**)

to the disease. Six died of progressive respiratory failure independent of efficacy of initial treatment [137].

The treatment of ILD in patients with Sjögren's syndrome is not well defined [139]. Hydroxycholoroquine has been shown to reduce sicca symptoms in a retrospective study [140] but its effect on pulmonary involvement was not evaluated. Deheinzelin reported the evolution of 11 patients treated with azathioprine alone or combined with prednisone [129]. The condition of seven patients improved (symptomatic relief and increase of vital capacity) and one patient deteriorated. Among five untreated patients, only one improved. The respective position of these treatments is not clear but a trial of prednisone and immunosuppressants should be performed in symptomatic patients. Improvement of ILD with rituximab has been reported in six out of eight patients treated in one series [141], but the characteristics of lung involvement were not precisely described in that study.

Lymphocytic Interstitial Pneumonia

With follicular bronchiolitis and BAL lymphocytosis, LIP is one of the pulmonary lymphoproliferative disorders associated with SS. LIP is a rare infiltrating pulmonary disorder. The definitive diagnosis requires a lung biopsy showing lymphoplasmocytic infiltration of the interstitial tissue and the alveolar septa, associated with lymphoid follicles and sometimes germinal centres [142]. Epithelioid and giant cell granulomas, and limited areas of organizing pneumonia, can be observed [142]. A coexistence with follicular bronchiolitis is possible; the final histopathological diagnosis will depend on the dominant component of the lesion. Histological diagnosis of LIP is sometimes difficult [142]. LIP must be differentiated from other lymphoid pulmonary infiltrations, mainly MALT (Mucosa Associated Lymphoid Tissue) lymphoma; this requires the use of immunohistochemical techniques (lymphocyte immunophenotyping) and molecular biology techniques (study of immunoglobulin gene rearrangements) to identify a clonal lymphocyte population. Other pulmonary disorders can be mistaken for LIP, in particular hypersensitivity pneumonitis or cellular NSIP. Sjögren's syndrome must be sought systematically, as SS is the cause of LIP in 25–50 % of cases [142–144].

The CT scan occasionally suggests the diagnosis when it shows centrilobular and subpleural nodules associated with ground glass opacities, and thickening of peribronchovascular tissues and the interlobular septa. Parenchymal cysts are present in more than one in two cases, and enlarged mediastinal lymph nodes variable in size are present in one case in two [143]. Limited areas of pulmonary consolidation are possible [143]. Few data are available concerning the evolution of LIP. In a study of 14 patients followed-up for 13 months, 9 patients improved, and 1 was stable, while 4 patients worsened and developed fibrotic lesions with honeycombing [145]. In another series, progression to respiratory failure was observed in 3 of the 15 patients studied (20 %) despite treatment [144]. The issue of a possible evolution of LIP to lymphoma has not been entirely settled. Some observations in the literature could correspond to undiagnosed MALT lymphomas.

The treatment of LIP is not well established. Corticosteroids are usually administered, sometimes associated with immunosuppressants (methotrexate, cyclophosphamide, azathioprine, cyclosporin) [144]. New treatments targeting B lymphocytes (rituximab) require further evaluation.

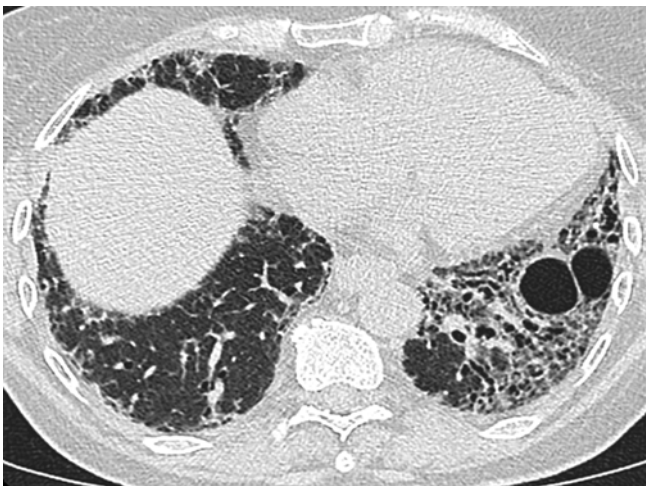

Fig. 26.14 A fibrotic pattern with lung cysts in a patient with primary Sjögren's syndrome

Cystic Lung Disease

The HRCT pattern in SS-ILD is not specific. However, cystic lesions are reported in about 30 % of the patients with SS, sometimes associated with LIP [145] (Figs. 26.11 and 26.14). It has been suggested that cysts form as a consequence of bronchiolar obstruction due to follicular bronchiolitis although this is uncertain [145, 146]. The presence of pulmonary cysts was associated with LIP by Ichikawa et al. in 1994 but cysts are also observed in SS without LIP [147]. The cysts are single or multiple, variable in size (from 5 to over 10 cm), with a thin or indiscernible wall. Their distribution is random, but they are often situated within the parenchyma. They sometimes include calcifications. With time, their size can reduce, remain stable, or increase. In rare cases, the cysts can become giant and cause chronic terminal respiratory failure [148]. In this context, the presence of nodules should also prompt a search for pulmonary lymphoma [149]. There is no specific treatment for cystic lung disease associated with SS, but lung transplantation has been performed in some cases.

Pulmonary Lymphoma

Patients with SS have an increased risk of developing a non Hodgkin lymphoma (relative risk: 6.5) [150, 151]. Sjögren's associated lymphoma is usually a B-cell non Hodgkin's lymphoma which arise primarily in the salivary glands, but also in mucosal sites including stomach and the lung. Pulmonary involvement occurs in 20 % of the patients with Sjögren's associated lymphoma [152]. Radiographical presentation may vary: chronic alveolar opacities, reticular or reticulonodular opacities, diffuse nodular lesions, or pleural effusion with or without mediastinal disease [153–155]. On high-resolution CT, cysts are characteristic in patients with lymphocytic interstitial pneumonia, whereas consolidation, large nodules, and pleural effusions are characteristic in patients with malignant lymphoma (Fig. 26.15). These findings on high-resolution CT help differentiate LIP from malignant lymphoma [156]. Pulmonary lymphoma may be indolent and surgically removed, may be controlled with cytotoxic drugs such as chloraminophene or cyclophosphamide, and may evolve to an aggressive disease requiring a systemic polychemotherapy with monoclonal B-cell antibodies [153–155, 157]. The nature and existence of pseudolymphoma, a tumor-like aggregate of lymphoid cells that does not meet the criteria for malignancy, is debated.

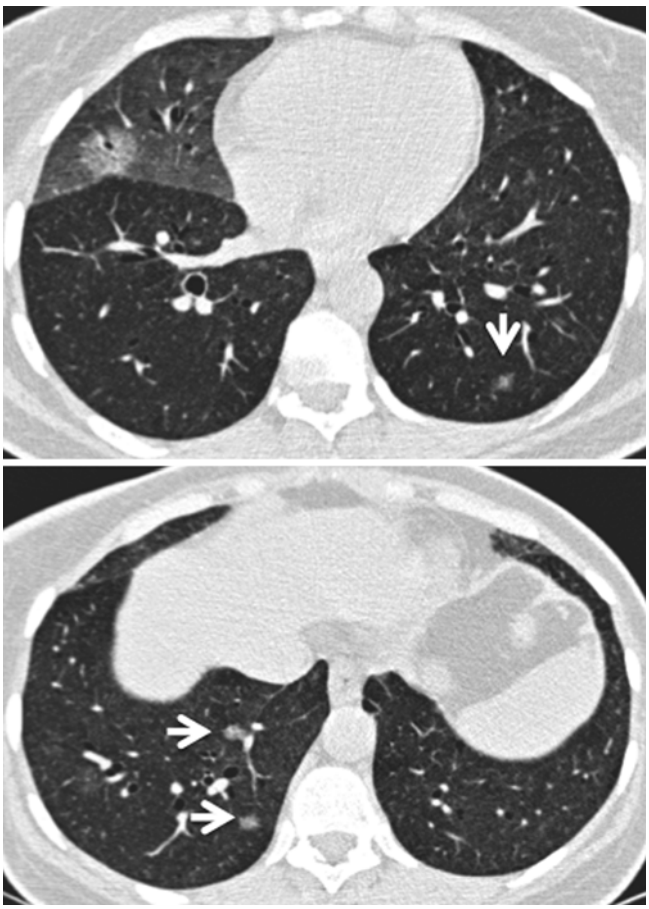

Fig. 26.15 Multifocal primary lung lymphoma in a patient with primary Sjögren's syndrome. Small nodules are marked with *arrows* in *upper* and *lower panel*

Pulmonary Amyloidosis

Amyloid-associated cystic lung disease presenting as nodules, sometimes calcified, in conjunction with cystic lesions, has been detected in a limited number of patients [149, 158].

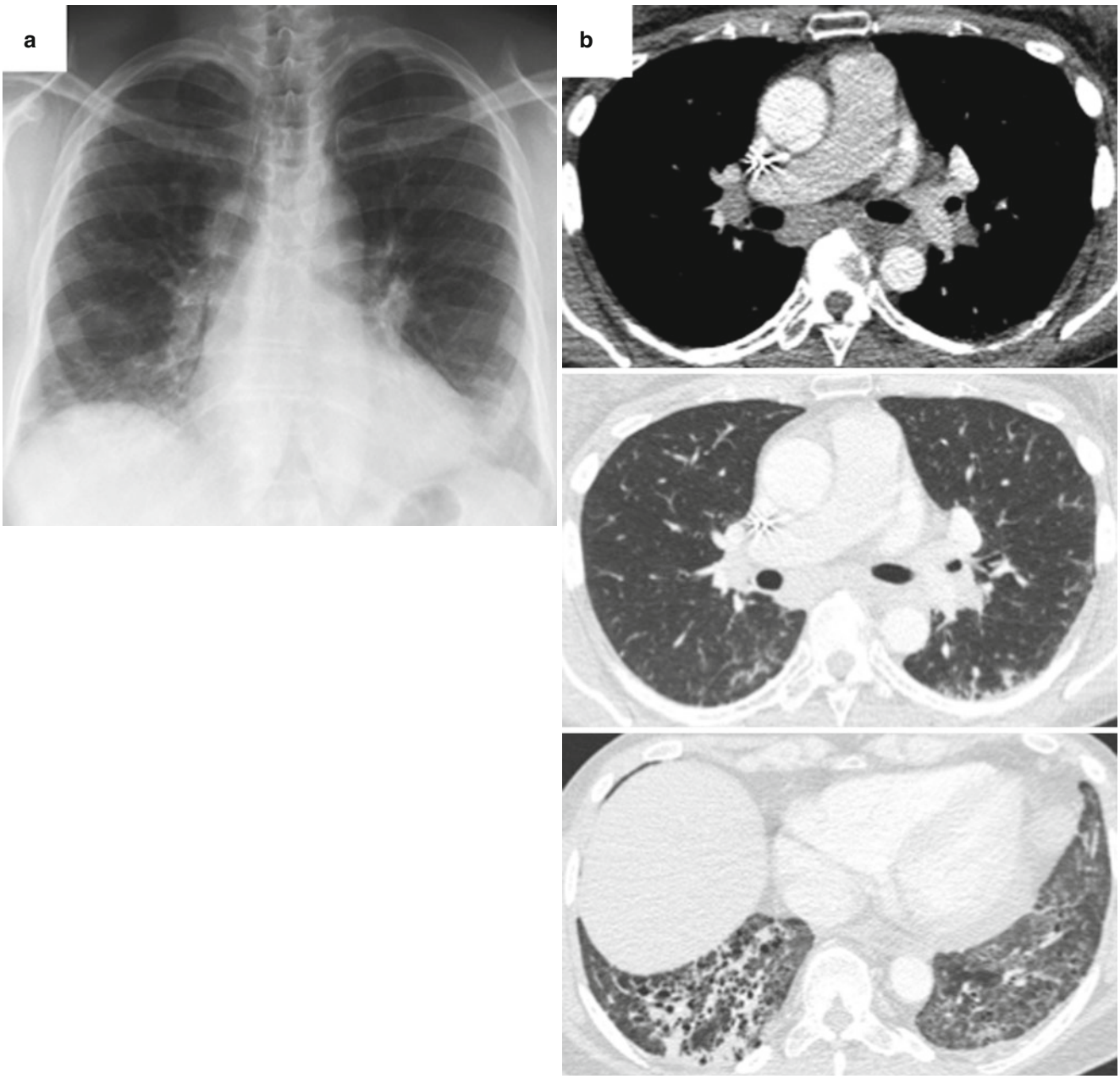

Fig. 26.16 Association of sarcoidosis and non specific interstitial pneumonia in a patient with primary Sjögren's syndrome. Chest X ray (panel **a**) and CT scan (panel **b**) demonstrate hilar and mediastinal adenomegaly, and a combination of reticulations and ground glass opacities with a subpleural and lower zones predominance. Surgical sampling of mediastinal lymph nodes through mediastinoscopy evidenced extensive non necrotizing tuberculoid granulomas. Lung tissue was obtained through videothoracoscopy and showed a pattern of non specific interstitial pneumonia

Pulmonary amyloid deposits are composed of amyloid light chains or AA protein, the most often localized in the lung, and exceptionally associated with systemic amyloidosis [159]. Mucosa-associated lymphoid tissue (MALT) lymphoma is associated in about 50 % of the patients [158]. PET scan performed in six patients did not reveal (18)F-2-deoxyglucose (FDG) uptake except in one nodule with borderline uptake [158].

Coexistence of Sjögren's Syndrome and Pulmonary Sarcoidosis

The revised classification criteria for SS exclude patients with sarcoidosis [117]. However, cases of SS coexisting with sarcoidosis have been described and clinically well recognized [160] (Fig. 26.16). A recent review regrouped 59 observations from the literature reporting the coexistence

of these two diseases in the same patient [161]. The frequency of sarcoidosis during primary SS has been estimated at 1 % [160, 161], which is far higher than the prevalence of sarcoidosis in the general population [162] and argues in favour of a pathophysiological connection between the two diseases, both characterized by considerable lymphocyte activation and a high prevalence of HLA-DR3. The diagnosis is made on the presence of antinuclear antibodies with anti-SSA or anti-SSB antibodies and non-granulomatous lymphocytic sialoadenitis in a patient with sarcoidosis [161]. The patients are the most often women (83 %). Mean age is 50. Both diseases are diagnosed at the same time in 60 % of cases. In 20 % of cases, the diagnosis of SS precedes that of sarcoidosis by 4 years on average. In 20 % of cases, the sarcoidosis is diagnosed on average 8 years before the SS [161]. Severe pulmonary hypertension with or without ILD [163] has been also reported.

Polymyositis and Dermatomyositis

Among the inflammatory myopathies, polymyositis and dermatomyositis are particularly associated with pulmonary involvement. While both polymyositis and dermatomyositis can share the same repertoire of specific antibodies and possess similar clinical patterns of muscle involvement, their divergent muscle histopathology suggests a different immunopathogenesis [164] (see Table 26.4 for classification criteria). Polymyositis appears to be a CD8+ predominant T-cell mediated assault on the myofiber, suggesting that the targeted antigen lies within the muscle surface. In contrast to polymyositis, dermatomyositis appears to be humorally mediated, with B-cells and CD4+ T cells located in a perivascular pattern leading to a perifascicular atrophy and fibrosis. Dermatomyositis and polymyositis are characterized by skeletal muscle inflammation and often involve the skin and lungs [113]. Skin findings in dermatomyositis include a violaceous erythematous rash over the interphalangeal joints, knuckles, elbows or knees (Gottron sign), eyelids (heliotrope rash), or nape of the neck and upper chest or upper back and shoulders [165]. Some patients have amyopathic dermatomyositis characterized by minimal to no muscle involvement yet severe ILD [166]. Pulmonary involvement may precede by many years, or occur simultaneously or follow the muscular manifestations of inflammatory myopathies [167, 168]. The variable and subtle presentations of these patients, requiring a high index of suspicion for the presence of ILD in the setting of myositis and for dermatomyositis or polymyositis in patients with seemingly idiopathic ILD or ARDS (see Table 26.6 for suggested investigations in a patient with ILD and suspected myositis). In addition to creatine kinase and electromyogram, detection of inflammatory lesions by f-18 fluorodeoxyglucose positron emission tomography [169] or MRI of proximal muscles [170] may aid in diagnosis and guide muscle biopsy.

Table 26.4 Diagnostic criteria for Dermatomyositis and Polymyositis [204]

1. Symmetric weakness of proximal muscles with or without dysphagia or respiratory muscle involvement.
2. Characteristic histopathologic findings on skeletal muscle biopsy sample
3. Elevation of skeletal muscle enzymes: creatine kinase, aldolase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase
4. Characteristic findings on electromyography
5. Dermatologic features, including: (a) Heliotrope discoloration of the eyelids with periorbital edema (b) Scaly, erythematous dermatitis over the dorsa of hands especially metacarpophalangeal and proximal interphalangeal joints (c) Involvement of the knees, elbows, medial malleoli, face, neck, and upper torso
Definite myositis: 4 criteria (without the rash) for PM, 3 or 4 criteria (plus the rash) for DM.
Probable myositis: 3 criteria (without the rash) for PM, 2 criteria (plus the rash) for DM.
Possible myositis: 2 criteria (without the rash) for PM, 1 criterion (plus the rash) for DM.

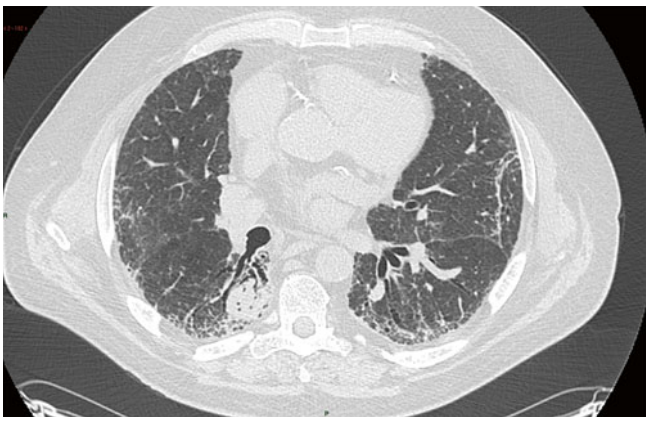

Fig. 26.17 A lung carcinoma was detected in the right lower lobe in a fibrotic area, at the time of diagnosis of dermatopolymyositis

Beside ILD, different elements of the respiratory system may be involved in patents with inflammatory myopathies: respiratory muscles dysfunction [171], lung cancer [172] (Fig. 26.17), aspiration pneumonia in patients with pharyngolaryngeal muscles involvement, pulmonary hypertension [173]. Cardiac involvement is common and may induce dyspnea and chest X ray abnormalities. Pulmonary involvement is a predominant cause of death, due to aspiration pneumonia (particularly in elderly patients), to the evolution of

pulmonary fibrosis or to lung cancer [168, 174]. Statins may induce a reversible syndrome of inflammatory myopathy and lung involvement [175]; therefore, a careful evaluation of drug exposure is mandatory.

Serological Classification

Although the pathological mechanisms of muscle injury appear to be different between DM and PM, both share a repertoire of antibodies associated with unifying extramuscular manifestations. The prevalence of autoantibodies in patients with acute inflammatory myopathies is much higher than was previously appreciated [176]. An important variant in the inflammatory myopathies is the antisynthetase antibody syndrome, which is defined by a positive serologic test for one of the eight identified antiaminoacyl transfer RNA (tRNA) synthetase antibodies, such as anti-histidyl (anti-Jo1), antithreonyl (anti-PL7), anti-alanyl (anti-PL12), anti-isoleucyl (anti-OJ), anti-glycyl (anti-EJ), anti-asparaginyl (anti-KS), anti-phenylalanyl (anti-Zo) and anti-tyrosyl-tRNA (anti-YRS) synthetase antibody, and one or more of the following: myositis (60–100 %), ILD, arthritis, Raynaud phenomenon, or erythema, hyperkeratosis, and cracking of the lateral aspects of the fingers (mechanic's hands) [177, 178]. Severe constitutional symptoms are common, with fever in 80 % of the patients, asthenia and weight loss. Anti-Jo1 antibody is the more common of antisynthetase antibodies, being encountered in 60–80 % of patients with antisynthetase antibody; on the other hand, anti-PL7 and anti-PL12 antibodies are less frequent, being reported in 10–15 % and 5–10 %, respectively, of patients with antisynthetase antibody. Among the clinical manifestations, ILD is the most frequent complication of antisynthetase antibody syndrome, occurring in 70–89 % of patients [168]. In patients with antisynthetase antibody syndrome, ILD has been found to result in increased morbidity and mortality [179, 180].

Clinical presentation may vary according to the antisynthetase antibody. In one study, the presence of anti-Jo1 antibody resulted in more severe myositis, joint impairment and increased risk of cancer, whereas the presence of anti-PL7/PL12 antibody was associated with early and severe ILD, and gastrointestinal complications [168]. In a study including anti-Jo1 (n = 160), anti-PL7 (n = 25) and anti-PL12 (n = 48) patients, ILD was more frequent (80 % and 88 % vs 67 %, p = 0.014) whereas myositis was less common (44 % and 47 % vs 74 %, p < 0.001) in patients with anti-PL7 and anti-PL12 compared to anti-Jo1 [180]. In that study, patient survival was significantly lower in patients with anti-PL7/12 rather than anti-Jo1 [180].

The diagnostic value of the detection of antisynthetase antibodies has been challenged since anti-PM/Scl and antisynthetase antibodies are associated with similar clinical manifestations, with the exception only of more overt myositis with anti-synthetase antibodies [181]. Troyanov and colleagues classify together under the term of « overlap myositis » all patients with inflammatory myopathy and detection of an overlap antibody (including antisynthetase; anti-systemic sclerosis-associated antibodies (such as anti-RNP, anti-PMScl, anti-Ku); anti-signal recognition particle, anti nucleoporins) [182]. Recently, anti-melanoma differentiation-associated gene 5 antibody (anti-MDA5) (also known as anti-clinically amyopathic dermatomyositis 140, anti-C-ADM-140) has been associated with acute/sub acute and rapidly evolving ILD [183–185].

Patterns of Interstitial Lung Disease

Interstitial lung disease affects 30–45 % patients and is usually present at the time of diagnosis [113]. Up to 30 % of the patients will never have evidence of myositis [174]. Antisynthetase antibodies are detected in 40–80 % of the patients with polymyositis and ILD (anti-Jo1 being the most frequent) [186, 187]. Anti-Jo1 is present in 23 % of all patients with polymyositis. Arthritis is more common in inflammatory myopathies with ILD [188, 189]. Pulmonary involvement bears a poor prognosis leading to the death with respiratory insufficiency in 30–66 % of patients.

Interstitial lung disease may take several forms:

- an acute respiratory failure evolving in a few days or weeks with fever, bilateral and basal infiltrative opacities and a negative search for pathogens and a failure of empirical antibiotics. Histopathology reveals a diffuse alveolar damage [190]. The prognosis is usually poor without improvement despite aggressive corticosteroids and immunosuppressants treatment. Some forms are responsive to corticosteroids. In that case, histopathology reveals NSIP, or organizing pneumonia (Fig. 26.18), sometimes associated [187]. Sometimes, the clinical pattern is that of an acute alveolar hemorrhage with pulmonary capillaritis [24] (Fig. 26.19). Acute presentation is seen most often in amyopathic dermatomyositis [166].
- a sub-acute and progressive ILD corresponding to organizing pneumonia or an overlap of organizing pneumonia and NSIP usually with a good initial response to corticosteroids, at least in part [187, 189]. However, most patients will deteriorate while decreasing the dose of corticosteroids and will require the adjunction of immunosuppressants.
- a chronic progressive fibrotic ILD, corresponding to fibrotic NSIP (Fig. 26.20) or UIP (Fig. 26.21), which tends to respond poorly to steroids and other forms of immunosuppressive therapy [187, 189]. About one third of the patients will deteriorate their lung function at follow-up and develop chronic respiratory failure, [168, 174, 189].

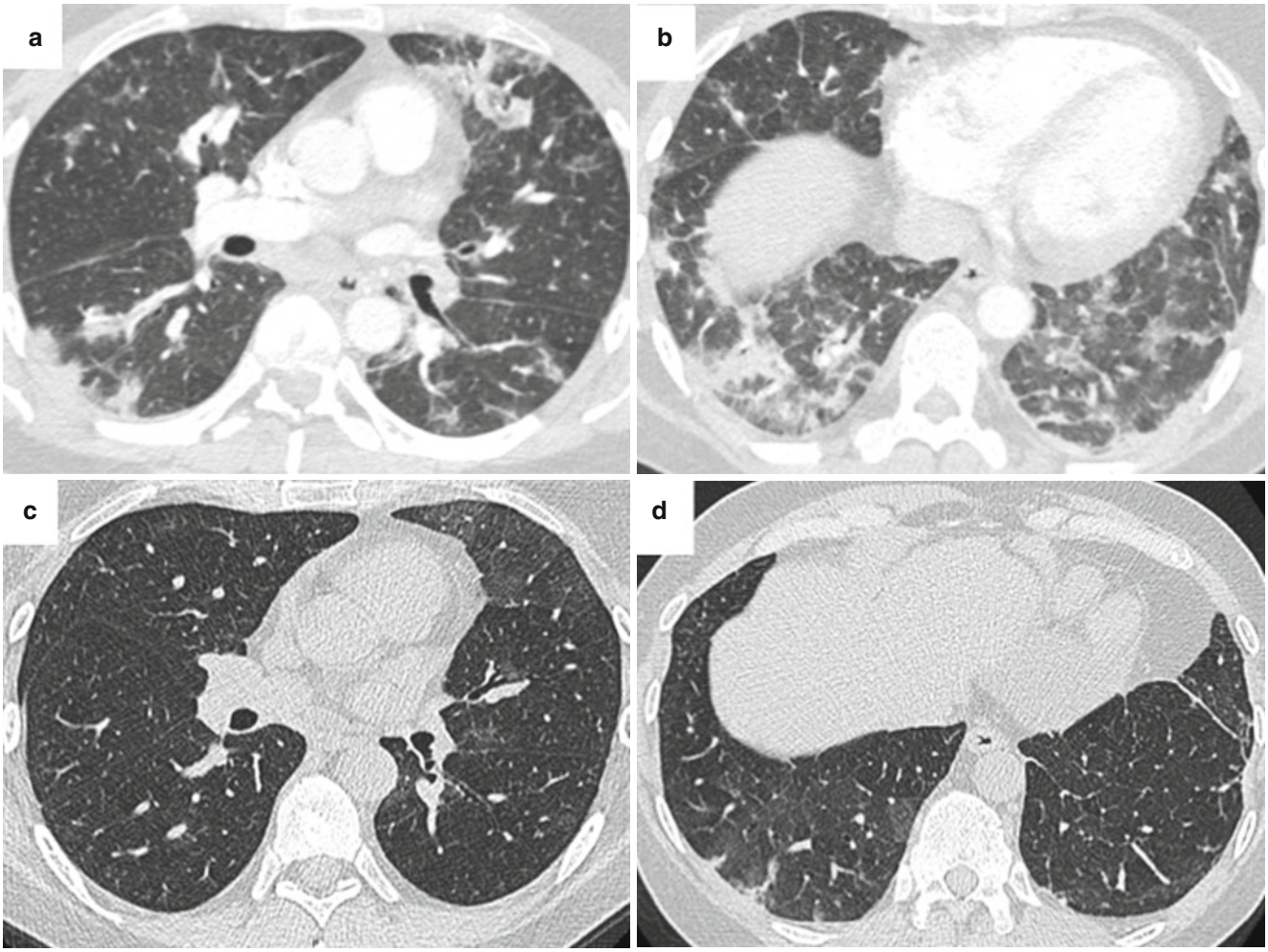

Fig. 26.18 Organizing pneumonia revealing polymyositis. Panel **a**, **b** show the CT obtained at diagnosis before initiation of therapy. Panel **c**, **d** show the follow up CT, after 4 months of corticosteroid treatment, with an almost complete resolution of abnormalities

Pulmonary function tests indicate a restrictive defect with reduced diffusing capacity for carbon monoxide, and hypoxemia at rest. Exercise testing is of importance in inflammatory myopathies patients to elucidate the cause of dyspnea. In some patients, the radiograph will detect lung infiltrates in a patient without symptoms. Alternatively, HRCT may demonstrate an ILD in a patient with normal radiograph.

Treatment of Interstitial Lung Disease

Corticosteroids are used for initial treatment (prednisone 40–60 mg/day), sometimes with methylprednisolone pulses. Oral or intravenous cyclophosphamide allow to stabilize lung function in patients with a progressive disease. In patients with a non progressive disease, mild immunosuppressive treatment based on azathioprine or mycophenolate mofetil allows for a fair control of the disease [187]. In refractory cases, methylprednisolone pulses, cyclosporine, and tacrolimus have been successfully used [191]. Anecdotal reports suggest that intravenous immunoglobulins may have a beneficial effect on lung involvement [192]. Rituximab (anti-CD20) may be a helpful therapy for refractory ILD associated with antisynthetase antibody, as reported in case reports [193] and in two retrospective series [194, 195]. Rituximab appeared to stabilize and/or improve the ILD in 7 of 11 patients in one report [194] and in all seven patients in another report [195].

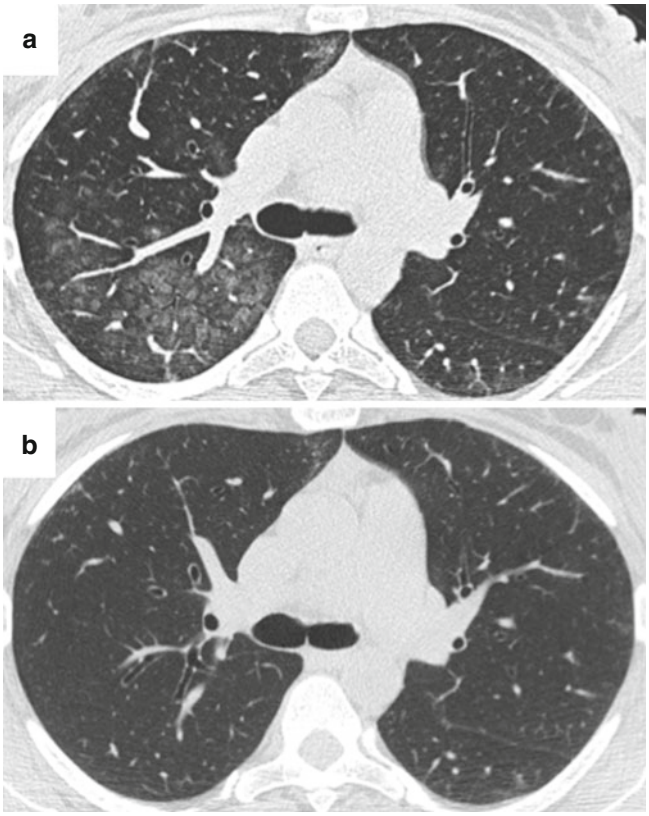

Fig. 26.19 Alveolar hemorrhage in a woman with polymyositis (panel **a**). Opacities resolved after treatment with corticosteroids (panel **b**)

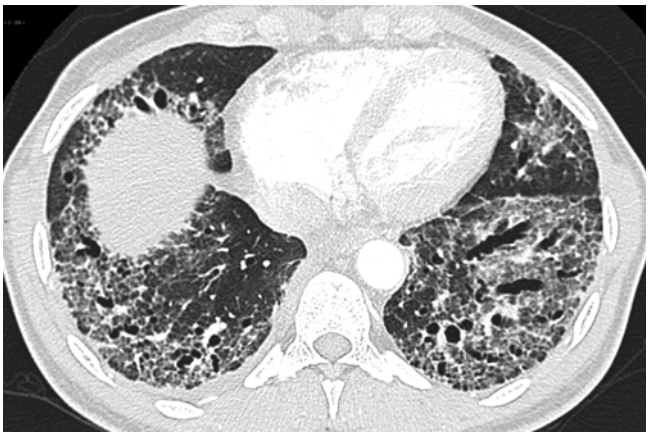

Fig. 26.20 NSIP pattern in a patient with ILD associated with an antisynthetase antibody

Others

Pneumothorax and pneumomediastinum can develop, usually in dermatomyositis or amyopathic dermatomyositis, and can reveal the inflammatory myopathy [196]. Severe pulmonary hypertension has been occasionally described in patients with inflammatory myopathies, with or without ILD [173, 197].

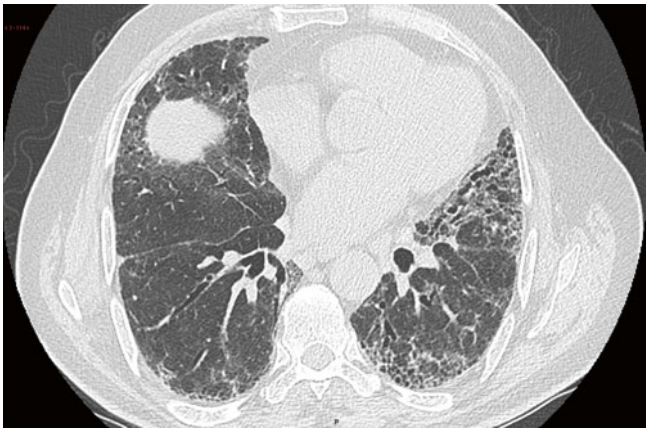

Fig. 26.21 UIP pattern in a patient with dermatopolymyositis

Mixed Connective Tissue Disease

Patients with mixed connective tissue disease (MCTD) exhibit clinical features of SLE, progressive systemic sclerosis, and inflammatory myopathies [198] (see Table 26.5 for classification criteria). A prerequisite for the diagnosis of MCTD is the presence of high titers of antibodies against uridine-rich RNA-small nuclear ribonucleoprotein (anti-RNP) [198]. The identification of MCTD as a separate entity remains debated since about 50 % patients initially diagnosed MCTD will evolve into a definite disease within 5 years [198] [199]. Although they were not reported in the original publication on MCTD, pleuropulmonary manifestations are common in MCTD and the incidence varies from 20–85 % [198, 199]. Respiratory and nonrespiratory features of the disease follow those seen in systemic lupus erythematosus, scleroderma, or inflammatory myopathies. Major respiratory manifestations include ILD and pulmonary fibrosis (20–65 %), pleural effusion (50 %), and pulmonary hypertension (10–45 %). Other pulmonary features consist of pulmonary vasculitis, pulmonary thromboembolism, pulmonary infections (secondary to aspiration pneumonia due to esophageal motility alterations and immunosuppression), alveolar hemorrhage, pulmonary nodules, pulmonary cysts, mediastinal lymphadenopathy, and respiratory muscles dysfunction. Pulmonary hypertension is a major cause of mortality and morbidity. Principles for diagnosis and treatment are similar to those described for SLE, scleroderma, and inflammatory myopathies.

Table 26.5 Diagnostic criteria for mixed connective tissue disease [198]

Kasukawa and Sharp [205]	Kasukawa et al. [206]	Alarcon-Segovia et al. [207]
A. Major criteria	A. Common symptoms	A. Serologic
1. Myositis, severe	1. Raynaud's phenomenon	1. Anti-U1RNP
2. Pulmonary involvement	2. Swollen fingers or hands	B. Clinical
(a) DLCO <70 %	B. Anti-U1RNP positive	1. Edema in the hands
(b) Pulmonary hypertension	C. Mixed symptoms	2. Synovitis
(c) Proliferative vascular lesions on lung biopsy	*1. SLE like findings*	3. Myositis
3. Raynaud's phenomenon or esophageal hypomotility	1. Polyarthritis	4. Raynaud's phenomenon
4. Swollen hands or sclerodactyly	2. Lymphadenopathy	5. Acrosclerosis
5. Anti ENA and anti-U1RNP positive and anti-Sm negative	3. Facial erythema	
B. Minor criteria	4. Pericarditis or pleuritis	
1. Alopecia	5. Leukopenia (<4,000/mm^3) or thrombocytopenia (<100,000/mm^3)	
2. Leukopenia	*2. Scleroderma-like findings*	
3. Anemia	1. Sclerodactyly	
4. Pleuritis	2. Pulmonary fibrosis, restrictive changes of lung (VC <80 %) or reduced DLCO <70 %	
5. Pericarditis	3. Hypomotility or dilatation of esophagus	
6. Arthritis	*3. PM-like findings*	
7. Trigeminal neuropathy	1. Muscle weakness	
8. Malar rash	2. Elevated serum levels of muscle enzymes (CPK)	
9. Thrombocytopenia	3. Myogenic pattern on EMG	
10. Mild myositis		
11. History of swollen hands		
Synthesis	**Synthesis**	**Synthesis**
At least 4 major criteria plus anti-U1RNP (exclusion criteria: positivity for anti-Sm); or 2 major criteria from among 1, 2 and 3, plus 2 minor criteria plus anti-U1RNP	At least one of the 2 common symptoms plus positive for anti-U1RNP plus 1 or more of the mixed symptoms in at least 2 of the 3 disease categories	Serologic criterion plus at least 3 clinical criteria, including either synovitis or myositis

Conclusion

Involvement of the respiratory system is a common event in connective tissue diseases. Although some characteristic clinical and radiological patterns are recognized, most of lung disorders may affect any type of connective tissue disease. Respiratory symptoms in a patient with a known CTD require a prompt and systematic work-up in order to diagnose specific diseases, and not to miss frequent and cardiorespiratory problems, such as pulmonary infections, pulmonary embolism, and left ventricular failure. Rare conditions such as drug-induced respiratory manifestations may prove difficult to diagnose.

Compared with idiopathic interstitial pneumonias, CTD-associated ILD are associated with a more favorable prognosis and, in some cases, may respond to immunosuppressive therapy. Thus, it is crucial to evaluate for underlying CTD in all patients presenting with ILD. Currently, there is little evidence to guide treatment strategies for patients with CTD in whom ILD develops. Some patients with CTD-ILD will be treated with immunosuppressive therapy directed toward nonpulmonary systemic manifestations of their CTD. Specific monitoring of pulmonary disease is necessary because the course of ILD does not always follow systemic disease activity.

Clinical Vignette

A 38 years old woman was admitted for dyspnea evolving for 6 weeks. The patient had been well until she went back from a 2 weeks trip to french indies. She experienced a progressively increasing dyspnea with pain in both legs. A prurit of the eye lids was attributed to an allergy to her make up.

On examination, she was polypneic at rest. Temperature was 37.8 °C. Bilateral crackles were heard. There was a pigmented edema of the eye lids (Fig. 26.22). Muscle strength testing was normal. Blood tests showed increased C Reactive Protein (23 mg/l) and increased CPK (threefold the upper limit of normal). Arterial blood gases analysis

showed hypoxemia (PaO_2 62 mmHg, $PaCO_2$ 37 mmHg, while breathing room air.) MRI of the lower limbs showed an abnormal signal in the muscles (Fig. 26.23). Chest X-ray (Fig. 26.24a) showed an elevation of the diaphragm with basal opacities in both lungs. Chest CT scan showed areas of consolidation predominant in the lower lobes (Fig. 26.3b). A diagnosis of dermatopolymyositis was suspected. A muscle biopsy was performed in the right quadriceps and confirmed the diagnosis. Autoimmune testing identified an anti-SSA antibody but no other antoantibody. The patient was treated with corticosteroids. A rapid improvement was obtained. Chest X-ray and CT scan improved (Fig. 26.3c, d) although some opacities persisted.

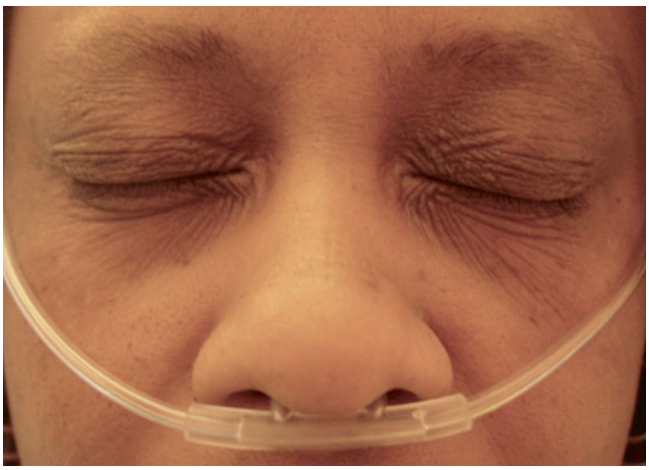

Fig. 26.22 Pigmented edema of the eyelids in a woman with dermatomyositis

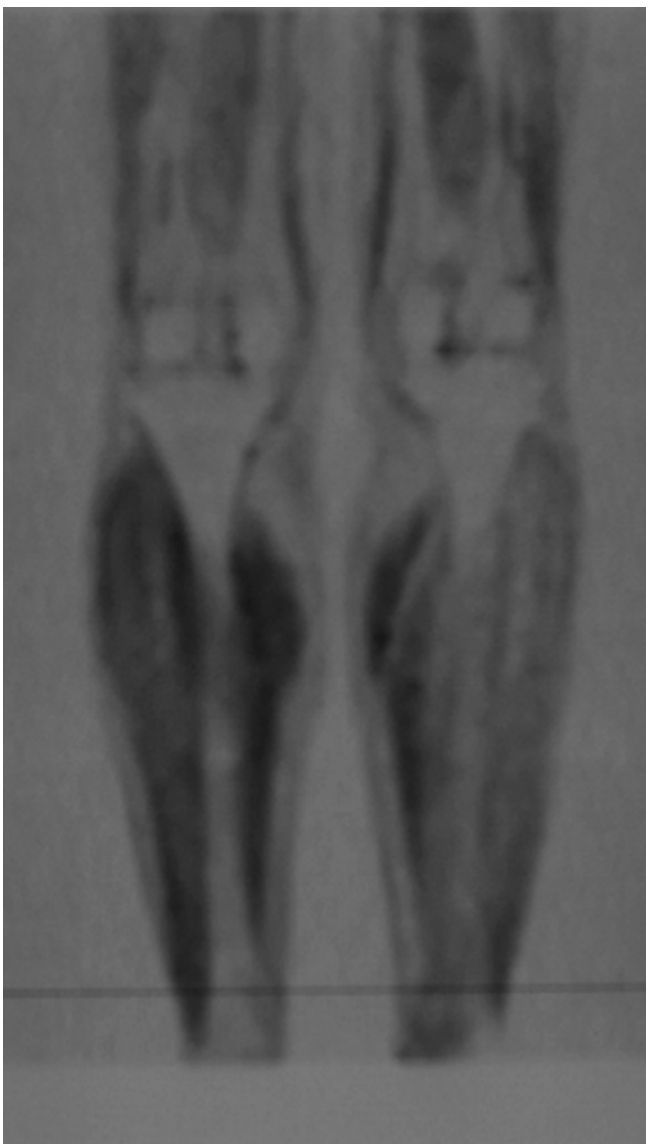

Fig. 26.23 MRI: Muscle hypersignal in the same patient as in in figure 26.22

Table 26.6 Suggested investigations in a patient with ILD and possible inflammatory idiopathic myopathy

1. Clinical investigations
(a) Search for other extra-pulmonary symptoms, including cutaneous signs suggestive of dermatomyositis
(b) Complete muscle testing
(c) Search for masked drugs with possible muscle side effects (e.g. fibrates, statins)
2. Biological investigations
(a) Muscular enzymes: Creatine kinase blood level determination
(b) Autoimmune screening
Antinuclear antibodies
Anti-SSA (antiRo52, antiRo60)
Myositis specific antibodies
Anti synthetase antibodies : anti-Jo1, anti-PL7, anti-PL12 (routinely performed); the search for less frequent anti-synthetase antibodies (anti-OJ, anti-EJ, anti-KS, anti-Zo, anti-YRS) requires specialized immunology laboratories
Anti-Srp, anti-Mi1, anti-Mi2,
Anti-MDA5
Anti-TIF1γ
Systemic sclerosis-associated antibodies:
Anti-Ku
Anti-PMScl
Anti-U1RNP
Anti-fibrillarin
Anti-nucleoporin
Anti-topoisomerase
Anti-centromeres
3. Imaging
(a) Whole body MRI (for identification of involvement muscles)
(b) Fluorine-18-fluorodeoxyglucose TEP (detection of muscle involvement and unknown cancer)
4. Electromyography
5. Muscle biopsy (in an abnormal muscle as evidenced by clinical symptoms, imaging or electromyography)

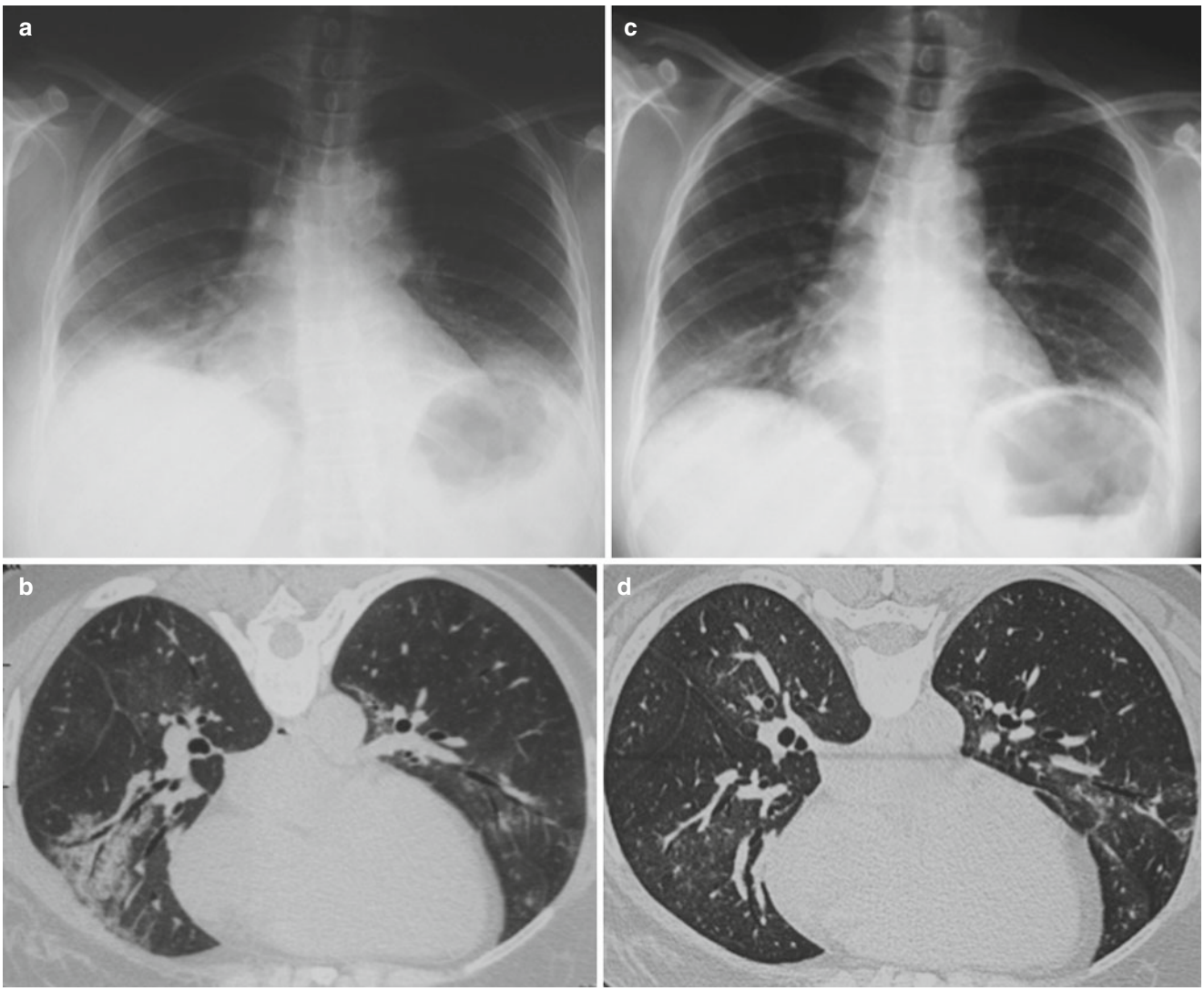

Fig. 26.24 Multifocal bilateral pulmonary consolidations (*left panel*) resolving with corticosteroids (*right panel*) in a woman with dermatomyositis (same patient as in in figure 26.22)

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Interstitial Lung Disease in Undifferentiated Forms of Connective Tissue Disease

27

Aryeh Fischer and Kevin K. Brown

Clinical Vignette

A 45 year-old woman, never smoker, presents with the relatively acute onset of dyspnea and also reports a dry cough that is worse with exertion and at night. Her past medical history is notable only for hypertension and hypothyroidism. On symptom review she describes low-grade fevers of several weeks duration, and she has noticed generalized puffiness of the hands for the past several months. She also describes a several month history of sensitivity and blanching of the hands on exposure to cold. On physical examination, she is noted to have digital edema and mild distal digital fissuring but no evidence of Raynaud's phenomenon, sclerodactyly or telangiectasia. Her musculoskeletal examination is normal; no synovitis or muscle weakness is detected. She has audible crackles on respiratory examination limited to the lower lung zones bilaterally. Her high-resolution computed tomography images reveal evidence of diffuse lung disease with a bilateral, peripheral predominant distribution of ground glass opacifications (Fig. 27.1). There is no honeycombing. Laboratory testing is notable for a positive anti-nuclear antibody at high titer (1:1,280) and positive anti-La (SS-A) antibody. All other serologies and lab tests are normal.

Does this patient have connective tissue disease-associated interstitial lung disease?

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Introduction

The interstitial lung diseases are a heterogeneous group of disorders that diffusely affect the pulmonary parenchyma and are classified together based on specific clinical, radiological, and histopathological features [1]. While these diseases often occur as clinically isolated, they commonly arise within the context of an underlying connective tissue disease (CTD) [2]. Excluding an associated CTD is probably the most important and challenging step in diagnosing idiopathic pulmonary fibrosis (IPF) and a multidisciplinary approach – that includes the rheumatologist – is often useful when assessing for CTD in patients with suspected IPF.

The designations "connective tissue disease" or "collagen vascular disease" are used interchangeably and refer to the spectrum of systemic autoimmune diseases that are characterized by autoimmune phenomena (e.g. circulating autoantibodies) and autoimmune-mediated organ damage (Table 27.1). Although these disorders are grouped together, there is significant heterogeneity of clinical features associated with each of the specific CTDs. In addition to well-characterized forms of CTD, it is not uncommon for individuals to have incomplete or partial forms with clinical features that fall short of fulfilling existing classification criteria for a specific disease – resulting in a clinical diagnosis of "undifferentiated CTD" [3].

As a general rule, CTD manifests with autoimmune-mediated organ dysfunction with the lungs as a frequent target. There are multiple pulmonary manifestations; essentially every component of the respiratory tract is at risk of injury (Table 27.2). Furthermore, specific CTDs are often associated with specific patterns of lung involvement (Table 27.3). Certain CTDs are more likely to be associated with parenchymal disease, (e.g. systemic sclerosis [SSc] and poly-/dermatomyositis [PM/DM]), but all patients with CTD are at risk, and there is an expanding appreciation that ILD may be the first or only manifestation of a CTD [5–9]. Much less is known, and significant controversy exists, regarding the lung

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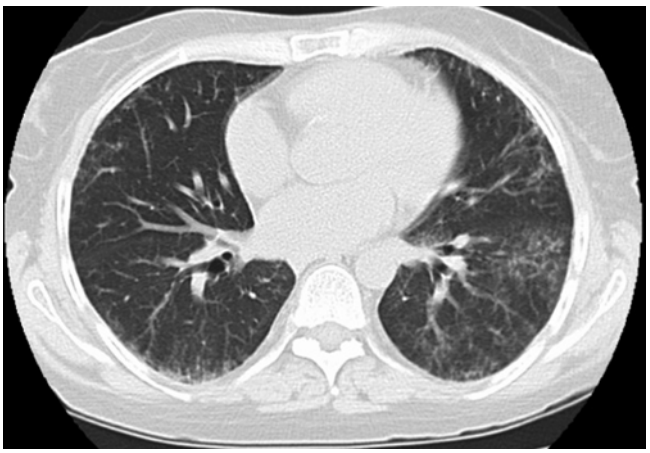

Fig. 27.1 High resolution computed tomographic image demonstrating bilateral, peripheral predominant ground glass opacifications suggestive of non-specific interstitial pneumonia

Table 27.1 Connective tissue diseases and other rheumatologic diseases associated with lung disease

Connective tissue diseases
Rheumatoid arthritis
Systemic lupus erythematosus
Systemic sclerosis
Primary Sjögren's syndrome
Polymyositis/dermatomyositis/anti-synthetase syndrome
Mixed connective tissue disease
Undifferentiated connective tissue disease
Other "rheumatologic" disorders
Systemic vasculitis
Polyangiitis with granulomatosis (Wegener's)
Microscopic polyangiitis
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
Spondyloarthropathy
Relapsing polychondritis
Behçet's disease
Anti-phospholipid syndrome

Table 27.2 Primary and secondary pulmonary manifestations of connective tissue diseases

Primary manifestations
Pleural
Pleurisy
Effusion/thickening
Airways
Upper
Cricoarytenoid disease
Ttracheal disease
Lower
Bronchiectasis
Bronchiolitis
Vascular
Pulmonary arterial hypertension
Vasculitis
Parenchymal
Interstitial lung disease
Diffuse alveolar hemorrhage
Acute pneumonitis
Rheumatoid nodules
Secondary manifestations
Infections
Drug-toxicity
Malignancy
Thromboembolism

Table 27.3 Most common CTD-associated pulmonary manifestations [4]

	SSc	RA	Primary Sjögren's	MCTD	PM/DM	SLE
Airways	–	++	++	+	–	+
ILD	+++	++	++	++	+++	+
Pleural	–	++	+	+	–	+++
Vascular	+++	–	+	++	+	+
DAH	–	–	–	–	–	++

The number of + signs indicates relative prevalence of each manifestation

SSc systemic sclerosis, *RA* rheumatoid arthritis, *CTD* connective tissue disease, *MCTD* mixed connective tissue disease, *PM/DM* polymyositis/dermatomyositis, *SLE* systemic lupus erythematosus, *ILD* interstitial lung disease, *DAH* diffuse alveolar hemorrhage

manifestations associated with partial or undifferentiated forms of CTD.

Thus, the intersection of ILD and CTD is complex and includes any of the following scenarios: (i) the identification of ILD within established, well-characterized forms of CTD, (ii) ILD as the presenting manifestation of a well-characterized form of CTD, or (iii) ILD that arises within the context of a suggestive, or undifferentiated, form of CTD. In this chapter, we review the clinical aspects of these intersecting conditions and focus especially on the latter two with ILD as the presenting manifestation of either well-characterized or undifferentiated forms of CTD.

Implications of a Diagnosis of CTD-ILD

There are numerous implications of a diagnosis of CTD-associated ILD (CTD-ILD). Most significantly, well-characterized forms of CTD-ILD, such as SSc-associated ILD, appear to have a more favorable prognosis than the idiopathic interstitial pneumonias (IIP) [10, 11]. (Far less is known about whether a similar survival benefit is seen in undifferentiated forms of CTD-ILD and this will be discussed in subsequent sections.) Other implications include providing a clinical explanation for otherwise unexplained extra-thoracic manifestations (e.g. Raynaud's phenomenon,

esophageal hypomotility, myositis) and highlighting a need for surveillance for other disease features (e.g. pulmonary arterial hypertension screening in SSc or malignancy surveillance in PM/DM), and guiding therapeutic decisions. Research implications include providing a precise phenotype to allow more effective pathobiology and natural history studies hopefully leading to the development of novel, targeted therapeutics. Indeed, among the most significant challenges encountered with CTD-ILD is that few effective therapeutic options exist, these conditions have been the target of few adequately powered and designed placebo-controlled trials, and there remains a poor understanding of the natural history of the disease.

ILD Within Pre-existing CTD

It is common to detect ILD in patients with pre-existing, well-characterized forms of CTD. Indeed, recent studies of CTD cohorts have shown radiographic prevalence rates of subclinical ILD ranging from 33 to 57 % [12–16]. ILD is particularly common in patients that have SSc, PM/DM, RA, primary Sjögren's syndrome, and mixed CTD (MCTD). However, just because parenchymal lung disease is identified in a patient with CTD does not mean the two are inter-related. For example, the presence of pre-existing RA does not preclude, and may predispose toward, the development of lung injury due to other causes (e.g., infection and drug-induced pneumonitis). Because patients with pre-existing CTD are often treated with immunosuppressive agents, the finding of new pulmonary infiltrates in an immunocompromised host should raise strong suspicions for respiratory infection – with either typical or atypical pathogens. Consideration for drug-induced lung toxicity is warranted because many of the immunomodulatory and anti-inflammatory therapies – especially methotrexate, but also aspirin, non-steroidal anti-inflammatory drugs, sulfasalazine, leflunomide, and the anti-tumor necrosis factor alpha (TNFα) agents – are all associated with drug-induced pneumonitis [17–34]. In this regard, just as with any other patient that presents with parenchymal lung disease, a comprehensive evaluation is needed to explore all potential etiologies (e.g., infection, drug-toxicity, environmental and occupational exposures, familial disease, smoking-related lung disease, and malignancy). Determining whether the ILD is associated with the pre-existing CTD is decided through a process of elimination [4].

ILD as the First Manifestation of a CTD

Identifying occult CTD when confronted with a so-called "idiopathic" interstitial pneumonia is common. Indeed, a recent study reported that of 114 consecutive ILD patients evaluated at a tertiary referral center, 17 (15 %) were confirmed to have a new CTD diagnosis [35].

Table 27.4 Suggested categories of ILD patients who require further rheumatologic evaluation [4]

1. Women, particularly those younger than 50
2. Any patient with extra-thoracic manifestations highly suggestive of CTD i.e. Raynaud's phenomenon, esophageal hypomotility, inflammatory arthritis of the metacarpal-phalangeal joints or wrists, digital edema, or symptomatic keratoconjuctivitis sicca
3. All cases of NSIP, LIP, or any pathologic pattern with secondary histopathology features that might suggest CTD i.e. extensive pleuritis, dense perivascular collagen, lymphoid aggregates with germinal center formation, prominent plasmacytic infiltration
4. Patients with a positive ANA or RF in high titer (generally considered to be ANA >1:320 or RF >60 IU/mL), a nucleolar-staining ANA at any titer, or any positive autoantibody specific to a particular CTD i.e. anti-CCP, anti-Scl-70, anti-Ro, anti-La, anti-dsDNA, anti-Smith, anti-RNP, anti-tRNA synthetase

There is no standardized approach to the identification of CTD. Current practice for assessing its assessment includes a thorough history and physical examination and testing for circulating autoantibodies [1, 36]. Many tertiary centers have also found that a multi-disciplinary evaluation that includes rheumatologic consultation is useful. In practice, it is both unrealistic and impractical to have rheumatologic specialty evaluation for all cases of IIP, and certain guidelines for deciding when to obtain rheumatologic consultation have been suggested (Table 27.4) [4].

Confirming the presence of a specific CTD in the absence of characteristic clinical findings is challenging [37]. Homma and colleagues evaluated whether interstitial pneumonia as the sole presentation of CTD can be differentiated from an IIP [38]. They described 68 patients who had presented with an IIP and were followed prospectively over 11 years. Thirteen patients (19 %) eventually developed classifiable CTD. The prevalence of a positive rheumatoid factor (RF) or anti-nuclear antibody (ANA) was no different in the group that developed clinically apparent CTD compared with those that did not. The authors concluded that patients defined as having an IIP cannot be distinguished from those with CTD-ILD before the systematic manifestations appear [38].

Although we recognize that detecting occult CTD is challenging and that ANA and RF positivity alone are not very useful, a thorough evaluation for subtle extra-pulmonary features of CTD, assessing a broader array of specific autoantibodies (Table 27.5) (and incorporating ANA titer and pattern of immunofluorescence), as well as consideration of radiographic and histopathologic features are all important components of an evaluation and make it more likely that occult CTD will be detected [8]. Moreover, and as the following studies will attest, a multidisciplinary approach – that includes the rheumatologist – can be useful when assessing the ILD patient for underlying CTD.

Table 27.5 Useful antibodies for CTD-ILD assessment

Autoantibody	Commonly associated CTD
High titer ANA (>1:320 titer)	Many
High titer RF (>60 IU/mL)	RA, Sjögren's disease, SLE
Anti-CCP	RA
Anti-centromere	Systemic sclerosis
Anti-nucleolar-ANA	Systemic sclerosis
Anti-Ro (SS-A)	Many
Anti-La (SS-B)	SLE, Sjögren's disease
Anti-Smith	SLE
Anti-ribonucleoprotein	SLE, MCTD
Anti-dsDNA	SLE
Anti-topoisomerase (Scl-70)	Systemic sclerosis
Anti-tRNA synthetase antibodies	Poly-/dermatomyositis (anti-synthetase syndrome)
Anti-PM-Scl	Systemic sclerosis/myositis overlap
Anti-Th/To	Systemic sclerosis
Anti-U3 ribonucleoprotein	Systemic sclerosis
ANCA	Systemic vasculitis

Fischer and colleagues retrospectively reviewed a cohort of 285 subjects with biopsy proven UIP that were considered to have IPF [39]. Twenty-five subjects (9 %) were found to have ANA positivity with a nucleolar-staining pattern, and of these, 13 also had a positive Th/To (nucleolar antibody highly specific for SSc) [40] antibody. Retrospectively, most of the subjects with nucleolar antibody positivity, and especially those with Th/To antibody positivity, had subtle extra-pulmonary features of SSc that included digital edema, Raynaud's phenomenon, telangiectasia, and esophageal hypomotility. The authors concluded that because these individuals had autoantibody positivity known to be highly specific for SSc, extra-pulmonary features suggestive of SSc, and a parenchymal injury pattern seen in SSc, these individuals likely had SSc rather than IPF [39]. This same group also described six individuals evaluated over a 12 month period for idiopathic NSIP or UIP [41]. All had nucleolar-pattern ANA positivity along with either Th/To or Scl-70 positivity and all had some extra-pulmonary features of SSc including telangiectasia, Raynaud's phenomenon, digital edema, or esophageal hypomotility. This small cohort further reinforced the notion that ILD may be the presenting manifestation of SSc and that strong suspicions for SSc are warranted – and extra-pulmonary features for SSc should be sought – in patients with nucleolar-pattern ANA and NSIP or UIP patterns of lung injury.

Mittoo and colleagues retrospectively evaluated a cohort of 114 consecutive patients referred to a tertiary referral center for ILD evaluation [35]. Thirty-four subjects (30 %) were found to have CTD-ILD and of these only half had presented with established, pre-existing CTD. Of the 17 identified to have an underlying CTD, 10 had PM/DM, 3 had systemic lupus erythematosus (SLE), 1 each with SSc and polyangiitis with granulomatosis (Wegener's) and 2 with undifferentiated forms of CTD. They found that younger age, high-titer ANA, and elevated muscle enzymes were associated with underlying CTD [35].

Further highlighting the importance of a multi-disciplinary evaluation, Castelino and colleagues described a cohort of 50 patients with ILD evaluated over a 1 year period at a tertiary referral center [42]. Of the 25 patients with a final diagnosis of CTD-ILD, 28 % had been initially referred with a diagnosis of IPF. Among those referred with CTD-ILD, 36 % had their diagnosis changed to an alternate CTD. In total, the diagnosis was changed in 54 % of the cohort [42]. Fischer and colleagues described a cohort of nine patients evaluated over a 2 year period with idiopathic NSIP that were ANA negative but found to have the anti-synthetase syndrome based on the presence of a tRNA synthetase antibody, NSIP, and subtle extra-pulmonary features that included "mechanic's hands", Raynaud's phenomenon, inflammatory arthritis, myositis, or esophageal hypomotility [43]. Interestingly, and characteristic of the anti-synthetase syndrome, these individuals were all ANA and RF negative. The authors emphasized the utility of cross-specialty evaluation of otherwise idiopathic ILD and that heightened suspicion for an underlying CTD is warranted in cases of NSIP – even when the ANA and RF are negative – and that assessing tRNA synthetase antibodies may help identify occult presentations of anti-synthetase syndrome [43]. Similarly, Watanabe and colleagues screened 198 consecutive cases of IIP with a panel of anti-tRNA synthetase antibodies and identified positive anti-synthetase antibodies in 13 cases (7 %) [44]. They reported that those with positive antibodies were younger and more likely to have NSIP or UIP with lymphoid follicules. Furthermore, among the 13 with a positive tRNA synthetase antibody, extra-pulmonary manifestations of anti-synthetase syndrome were retrospectively identified in seven cases (54 %) [44].

Finally, two recent series have shown that ILD may also be the presenting manifestation of RA and that assessing for RA-specific autoantibodies in patients with IIP may identify an at-risk phenotype for later RA development [45, 46]. Gizinski and colleagues described a series of four patients with ILD, RF, and anti-cyclic-citrullinated peptide (CCP) positivity and no articular findings of RA [46]. All were male, former smokers, and the average age at time of diagnosis of ILD was 70 years. Three patients died within 2 years of diagnosis of progressive lung fibrosis and never developed articular symptoms consistent with RA; but one case met full criteria for the articular aspects of RA several months after stopping immunosuppressive treatment for ILD. In a more recent series, Fischer and colleagues described 74 subjects evaluated over a 2 year period with anti-CCP antibody positivity, lung disease, and no evidence

of RA or other CTD [45]. Most were women and former cigarette smokers. Four distinct radiographic phenotypes were identified: isolated airways disease (54 %), isolated parenchymal lung disease (14 %), mixed airways and parenchymal lung disease (26 %), and combined pulmonary fibrosis with emphysema (7 %). Among subjects with high-titer anti-CCP positivity (45 %), 3 developed the articular manifestations of RA within 2 years of surveillance: only 1 of the 3 ever smoked, 2 had isolated inflammatory airways disease, and 1 had combined airways and parenchymal lung disease. The authors highlighted that the lung disease in this cohort resembled that seen in established RA, lung disease may be the presenting manifestation of RA, and anti-CCP positivity in inflammatory airways or parenchymal lung disease may be a pre-RA phenotype [45].

Undifferentiated Forms of CTD-ILD (Table 27.6)

There is a growing appreciation that many patients with IIP have subtle features suggestive of an autoimmune etiology and these individuals quite often do not meet established classification criteria for existing CTDs [2, 8]. It has even been suggested that idiopathic NSIP is itself an autoimmune disease or is the lung manifestation of undifferentiated CTD (UCTD) [47, 48]. Because of the otherwise generally better survival associated with CTD-ILD, there may be an inherent desire to find reasons to define disease as CTD-ILD. In some of these individuals a serum autoantibody known to be highly specific for a certain CTD (such as anti-CCP with RA) may be present despite the absence of overt systemic features and this poses challenges to diagnostic precision. In contrast to the improved survival experience associated with well-characterized forms of CTD-ILD, it remains to be determined whether undifferentiated forms of CTD-ILD are associated with a better outcome.

Also controversial is when there is a "rheumatologic flavor" to the ILD, but one which falls short of fulfilling the requisite features to allow a specific rheumatological diagnosis to be made using currently accepted criteria. These patients, in whom it appears that the lung is either the lone, or most clinically-significant manifestation of an occult CTD, are suspected of having a systemic autoimmune disease based on the presence of circulating autoantibodies, specific histopathological features on surgical lung biopsy, or extra-thoracic manifestations and could be classified as having "*lung dominant CTD*" rather than "idiopathic" disease [8]. Furthermore, despite recognition that ILD may be the first manifestation of CTD, current rheumatologic classification criteria do not allow a specific CTD designation for *isolated* ILD.

Current strategies for identifying and classifying these types of patients are both controversial and inadequate. Proposed terminology to describe and classify such patients includes "lung-dominant CTD" [8], "UCTD" [48], and "auto-immune featured ILD" [49].

UCTD in the Rheumatology Literature

In addition to well-characterized forms of CTD, it is common to encounter patients that have partial or incomplete forms of CTD and these cases are often considered to have UCTD [3, 50–52]. The first descriptions of "undifferentiated diseases" were made in 1969 by Sabo [53]. In 1980, LeRoy proposed the concept of "undifferentiated connective tissue syndromes" to define early phases of CTDs mainly characterized by the presence of Raynaud's phenomenon and digital edema [54]. Over the subsequent years, UCTD has been generally defined as a condition manifesting with signs and symptoms suggestive of a CTD, along with ANA positivity, but not fulfilling existing rheumatologic classification criteria for any specific CTD [3, 50–52]. Mosca and colleagues have reported that about 60 % of patients with UCTD will remain undifferentiated, and that when evolution to defined CTD occurs, it usually does so within the first 5 years of disease [3, 50–52]. UCTD may evolve into any of the CTDs, but most often evolves into systemic lupus erythematosus (SLE). UCTD patients that do not develop a characterizable CTD are considered to have a mild clinical picture – or "stable" UCTD – characterized by the presence of arthralgias or arthritis, Raynaud's phenomenon, leukopenia, anemia, and dry eyes or dry mouth [3]. An important distinguishing characteristic of UCTD is that *no major organ involvement* (such as lung disease) has been described [3]. Because of the mild clinical picture, UCTD patients rarely require immunosuppressive therapies.

A recent expert review on UCTD distinguishes "monosymptomatic UCTD" comprised of single organ-dominant diseases (such as ILD) that do not fulfill specific CTD criteria from that of stable, mild "oligosymptomatic UCTD" [3]. The authors acknowledge that the concept of UCTD includes a wide spectrum of diseases ranging from 'organ-dominant' conditions, to "stable UCTD", to early CTDs, or mild forms of CTDs. They suggest that only persistently oligosymptomatic conditions – and not "organ dominant" disease – be classified as "UCTD". Mosca and colleagues have proposed the following preliminary classification criteria for UCTD: (i) signs and symptoms suggestive of a CTD, but not fulfilling criteria for defined CTDs, (ii) positive ANAs and (iii) a disease duration of at least 3 years [3].

UCTD in the Pulmonary Literature (Table 27.6)

The concept of UCTD has been of interest within the pulmonary community as well. In 2007, Kinder and colleagues proposed a broader and less specific set of UCTD criteria

Table 27.6 Proposed criteria for categories of suggestive forms of CTD-ILD [2]

Proposed category	Clinical features	Laboratory or histopathology findings
Undifferentiated CTD (stricter definition)	**One or more of the following symptoms**:	**One or more of these autoantibodies**:
(requires at least one clinical feature and one laboratory finding)	Dry eyes or dry mouth, Joint pain or swelling	ANA (high titer)
	Raynaud's phenomenon	RF (high titer)
	Proximal muscle weakness	Anti-Smith
	Morning stiffness	Anti-ribonucleoprotein
		Anti-dsDNA
		Anti-Ro
		Anti-La
		Anti-Jo-1
		Anti-topoisomerase (Scl-70)
		Anti-centromere
Undifferentiated CTD (broader definition)	**One or more of the following symptoms**:	**One or more of these laboratory abnormalities**:
(requires at least one clinical feature and one laboratory finding)	Dry eyes or dry mouth	ANA (any titer)
	Gastro-oesophageal reflux disease	RF
	Weight loss	Anti-Ro
	Recurrent unexplained fever	Anti-La
	Joint pain or swelling	Anti-Jo-1
	Rash	Anti-topoisomerase (Scl-70)
	Photosensitivity	Erythrocyte sedimentation rate (two times normal)
	Dysphagia	C-reactive protein elevation
	Nonandrogenic alopecia	
	Mouth ulcers	
	Raynaud's phenomenon	
	Morning stiffness	
	Proximal muscle weakness	
Lung-dominant CTD	**All of the following features**:	**4a. Any one of these autoantibodies**
(requires all three listed clinical features and either 4a or 4b)	1. NSIP, UIP, LIP, OP, DAD, (or DIP if no smoking history), as determined by surgical lung biopsy or suggested by HRCT *and*	ANA > 1:320 titer
	2. Insufficient extra-thoracic features of a definite CTD *and*	RF > 60 IU/mL
	3. No identifiable alternative aetiology for IP *and*	Anti-nucleolar ANA (any titer)
		Anti-centromere
		Anti-CCP
		Anti-Ro
		Anti-La
		Anti-dsDNA
		Anti-ribonucleoprotein
		Anti-Smith
		Anti-topoisomerase (Scl-70)
		Anti-tRNA synthetase
		Anti-PM-Scl
		4b. **OR at least two of these histopathology features**:
		Lymphoid aggregates with germinal centres
		Extensive pleuritis
		Prominent plasmacytic infiltration
		Dense perivascular collagen

Table 27.6 (continued)

Proposed category	Clinical features	Laboratory or histopathology findings
Autoimmune-featured ILD	**One or more of the following symptoms**:	**One or more of these laboratory abnormalities**:
(requires at least one clinical feature and one laboratory finding)	Dry eyes or dry mouth	ANA ≥ 1:160 titer
	Gastro-oesophageal reflux disease	RF
	Weight loss	Anti-Ro
	Foot or leg swelling	Anti-La
	Joint pain or swelling	Anti-Smith
	Rash	Anti-ribonucleoprotein
	Photosensitivity	Anti-dsDNA
	Dysphagia	Anti-topoisomerase (Scl-70)
	Hand ulcers	Anti-CCP
	Mouth ulcers	Anti-Jo-1
	Raynaud's phenomenon	Aldolase
	Morning stiffness	Creatine phosphokinase
	Proximal muscle weakness	

and applied these criteria to a cohort of patients with IIP [48]. Retrospectively, they identified 28 subjects with an IIP that met their proposed criteria for UCTD and compared these subjects with a control group of 47 subjects with an IIP that did not meet their criteria. Interestingly, those that they defined as having UCTD were more likely to be female, younger, and non-smokers and were more likely to have ground-glass opacities on HRCT and NSIP on surgical lung biopsy. In all, 88 % of those with idiopathic NSIP met their definition for UCTD, and led the authors to conclude that most patients previously classified as having idiopathic NSIP have clinical, serologic, radiographic, and pathologic characteristics of autoimmune disease and they proposed that idiopathic NSIP is the lung manifestation of UCTD [48]. Of note, the accompanying editorial by Kim and Nagai pointed out several limitations of this study and argued against accepting the conclusion that idiopathic NSIP is UCTD [55]. In particular, they emphasized that there was uncertainty in the diagnosis of UCTD and a concern for more false-positive cases because the authors modified the more traditional UCTD criteria – that requires autoantibody positivity – to include nonspecific inflammatory markers (C-reactive protein, creatine phosphokinase, aldolase, or erythrocyte sedimentation rate) [55].

More recently, Corte and colleagues have called into question the clinical relevance of defining ILD patients as having UCTD and specifically called into question the application of the broader, less-specific UCTD criteria proposed by Kinder and colleagues [56]. They retrospectively studied 45 patients with biopsy-proven NSIP and 56 patients with biopsy-proven UIP. They reported that CTD features are common in patients with IIP, with 31 % of NSIP and 13 % of IPF patients fulfilling the stricter, more traditional criteria for UCTD [56]. However, when the broader, less specific, criteria of Kinder for UCTD was applied, an astounding 71 % of NSIP and 36 % of IPF patients could be reclassified as having UCTD [48, 56]. Because of its lack of specificity, the authors argued against further implementation of the Kinder set of criteria to define UCTD in patients with ILD. Furthermore, the identification of UCTD by either criteria did not impact survival. Instead, Corte and colleagues devised an algorithm that was predictive of the presence of NSIP and improved survival consisting of the absence of typical HRCT features of IPF, a compatible demographic profile (women < 50) or the presence of Raynaud's phenomenon [56].

"Autoimmune-Featured ILD" (Table 27.6)

Vij and colleagues have described a cohort of UIP-predominant ILD patients retrospectively identified as having a possible form of CTD-ILD [49]. Among 200 patients that presented to an ILD referral center, 63 were considered to have "autoimmune- featured ILD" if they had a sign or symptom suggestive of a CTD, but with insufficient features to label as definite CTD, and a serologic test reflective of an autoimmune process. The cohort that met their case definition of autoimmune-featured ILD had a similar demographic profile as IPF: most were older (average age of 66 years) and male. The most common clinical symptoms in the autoimmune-featured ILD cohort were non-specific symptoms of dry eyes or dry mouth (57 %) and gastroesophageal reflux disease (44 %). Seventy-five percent of those that met their case definition for autoimmune-featured ILD had a lung injury pattern of UIP. Finally, the survival of those with autoimmune-featured ILD was similar to that of IPF, and worse compared to CTD-ILD [49]. Interestingly, and arguing against the inclusion of non-specific symptoms in the proposed criteria, only the presence of an ANA at >1:1,280 titer was associated with improved survival.

"Lung-Dominant CTD" (Table 27.6)

Fischer and colleagues have proposed a set of provisional classification criteria to define the cohort of individuals with suggestive forms of CTD-ILD as having "lung-dominant CTD" (LD-CTD) [8]. A classification of LD-CTD would be reserved for those cases where the ILD has a "*rheumatologic flavor*" as supported by specific autoantibodies or histopathologic features and yet does not meet criteria for a defined CTD based on the lack of adequate extra-pulmonary features to confer a diagnosis of definite CTD-ILD. The authors argued that implicit with the concept of LD-CTD is the recognition that specific autoantibodies and/or histopathologic features alone can be enough to classify a patient as having CTD-ILD. The presence of objective extra-pulmonary features highly suggestive of CTD (e.g., Raynaud's phenomenon, inflammatory arthritis) are important and will lend further support for an underlying CTD, but their absence should not preclude a classification of LD-CTD. The authors emphasized that their intent was that the concept of LD-CTD and the associated criteria should be viewed as provisional, and that they might serve as a platform for further multidisciplinary, multi-center investigations, including validation via prospective study [8].

A number of potential advantages to the introduction of this novel classification were suggested: (1) The criteria offered are objective and measurable. (2) Non-specific symptoms (such as dry eyes, myalgias, arthralgias, or gastroesophageal reflux disease), non-specific inflammatory markers (such as erythrocyte sedimentation rate or C-reactive protein), and low-titer ANA or RF are not included because of their high prevalence in patients without CTD. (3) Surveillance for evolution to characterizable forms of CTD is encouraged. (4) The diagnosis isolates them from the (default) category of IIP and provides a framework by which questions regarding this subset's natural history, pathobiology, treatment, and prognosis can be answered and (5) The classification allows their distinction from well-characterized forms of CTD, without attempting to redefine existing CTD categories (such as UCTD) [8].

Do Cohorts of Undifferentiated Forms of CTD-ILD Behave Like IIP or CTD-ILD?

Whether patients with undifferentiated forms of CTD-ILD have the same outcomes as well-characterized forms of CTD-ILD or as IIP is not known. Recent studies have attempted to address the implications for prognosis of these somewhat nebulous designations [2].

Corte and colleagues showed that although the application of the more specific UCTD criteria was significantly associated with a histopathological pattern of NSIP, it did not impact survival [56]. Fischer and colleagues evaluated the prognostic significance of a positive nucleolar-pattern ANA among a cohort of patients with biopsy-proven, so-called IPF. Although on retrospective assessment these individuals had subtle extra-pulmonary features suggestive of SSc rather than IPF, this cohort with a LD-CTD phenotype, had similar survival as IPF [39]. Similarly, Vij and colleagues showed that survival in their autoimmune-featured ILD cohort was similar to IPF and worse than CTD-ILD [49].

Song and colleagues compared secondary histopathological features among three groups of patients with biopsy-proven UIP: Group 1 (n = 39) comprised CTD-UIP; Group 2 (n = 27), antibody-positive (ANA or RF) idiopathic-UIP (i.e. antibody-positive IPF); and Group 3 (n = 34) with antibody-negative idiopathic-UIP (i.e. antibody-negative IPF) and showed that the presence of circulating autoantibodies is associated with specific "autoimmune" histopathological features, even in the absence of CTD [57]. Among those with CTD-UIP there were more germinal centers, plasma cells, and fewer fibroblast foci when compared with all subjects who had IPF. Interestingly, histopathological features differed between the sub-groups 2 and 3 of IPF depending on autoantibody status: although none of the antibody-positive IPF subjects (Group 2) had extra-pulmonary features of CTD, they had higher germinal center scores and more plasma cells than antibody-negative IPF subjects (Group 3). Notably, no histopathological features distinguished CTD-UIP (Group 1) from antibody-positive IPF (Group 2). Among those with IPF (Groups 2 and 3), antibody status did not predict survival, and these cohorts of antibody positive or negative IPF had a worse prognosis than CTD-UIP (Group 1) [57].

Taken together, our current, incomplete, knowledge does not allow definitive conclusions to be drawn from these retrospectively identified cohorts of patients with various forms of undifferentiated forms of CTD-ILD regarding differences in outcome. However, the interim conclusion based on the current literature would suggest there is no difference [2].

Moving Beyond the Interdisciplinary Divide

As recently expressed [2, 8], there is far too little interdisciplinary dialogue in this arena and the advancement of this field would be better served by efforts to bridge this divide. Having a consensus – from both the pulmonary and rheumatology communities – on precise CTD disease characterization and classification is needed to provide a significant step in the right direction of addressing the existing interdisciplinary divide. Importantly, any of the proposed terms or criteria should be viewed as provisional, and we believe these patients should be distinguished from established, well-characterized, forms of CTD-ILD because validation via

prospective study is needed to better understand the natural history of these individuals and whether they truly behave as "CTD-ILD". Well-organized prospective studies are needed to better answer a number of important questions that include: (a) are there specific autoantibodies that play a role in the evolution of less- to well-characterized forms of CTD? (b) does having antibody-positive ILD affect likelihood of survival irrespective of whether or not there is an associated CTD? (c) are there specific "autoimmune" histopathological features that are associated with survival irrespective of any association with CTD? (d) how can we devise and implement a more unified, consistent set of classification criteria to allow for multi-institutional collaborative studies of individuals with undifferentiated forms of CTD-ILD?

The Evaluation: Detecting Occult CTD

Demographics

The demographic information of a patient with an IIP should not be overlooked when considering the potential for underlying CTD. Several studies have shown that among those with an IIP, younger age is associated with the presence of underlying CTD or NSIP [35, 48, 56]. Also, because women of reproductive age are the highest risk group for the development of autoimmune diseases, a heightened suspicion for the presence of CTD is warranted in any young woman presenting with ILD. Take for example, the clinical scenario of a patient presenting with a chest imaging or histopathologic pattern of usual interstitial pneumonia (UIP): when present in a 40-year-old woman it is far more likely to represent CTD-ILD than IPF and yet when present in a 65-year-old man it is far more likely to represent IPF!

Clinical Features

A multidisciplinary approach, detailed review of systems and thorough physical examination are all helpful when assessing for underlying CTD. Standardized tools, such as patient questionnaires, may also be a useful component in the assessment for the presence of symptoms of CTD (e.g. the ILD questionnaire produced by the American College of Chest Physicians http://www.chestnet.org/memberResources/downloads/networks/IDLDquestionnaire.pdf). In the following sections we highlight certain specific clinical features that lend more support for underlying CTD than others:

Inflammatory Arthritis

The reporting of symmetric joint swelling or stiffness, or identifying synovitis on physical examination is very useful and suggests underlying CTD. Because inflammatory arthritis is encountered in all of the CTDs, autoantibody profiles may be needed to clarify which specific CTD is present.

Raynaud's Phenomenon

Of the CTD symptoms encountered in patients with IIP, perhaps none is as important as the presence of Raynaud's phenomenon. The presence of Raynaud's phenomenon is associated with a pattern of NSIP [56] and when identified in a patient with ILD should raise strong suspicions for underlying CTD in general, and SSc (with or without overt skin thickening) in particular. Indeed, Raynaud's phenomenon is encountered in nearly all patients with SSc and is a common finding in patients with PM/DM, anti-synthetase syndrome, primary Sjögren's syndrome, MCTD, SLE, and UCTD.

Performing nailfold capillary microscopy is useful when assessing a patient with Raynaud's phenomenon [58, 59]. In particular, the presence of dilated or tortuous capillary loops or significant areas lacking capillary loops (i.e. capillary dropout) may be suggestive of SSc or PM/DM (Fig. 27.2).

Cutaneous Manifestations: Sclerodactyly, Digital Edema, Palmar Telangiectasia, and "Mechanic's Hands"

The cutaneous manifestations of SSc and anti-synthetase syndrome are worthy of special mention in this regard because these two disorders are so commonly manifested with ILD and their extra-thoracic features are very specific and yet may be subtle. It is important to recognize that the "mechanic's hands" sign of anti-synthetase syndrome can be as subtle as only mild distal digital fissuring (Fig. 27.3), and that palmar telangiectasia may be limited to the finding of only a single or scattered few dilated capillaries (Fig. 27.4). Nonetheless, when such findings are present in a patient with an IIP, they are highly suggestive of occult CTD.

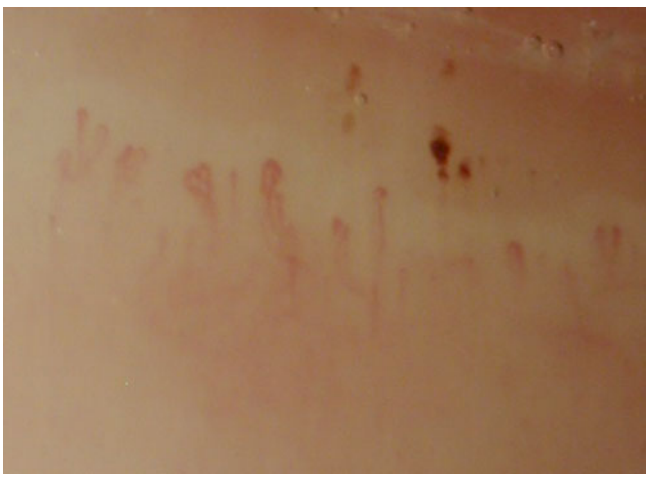

Fig. 27.2 Nailfold capillary microscopic image in a patient with systemic sclerosis demonstrating capillary loop tortuosity, dilation, and areas of dropout [4]

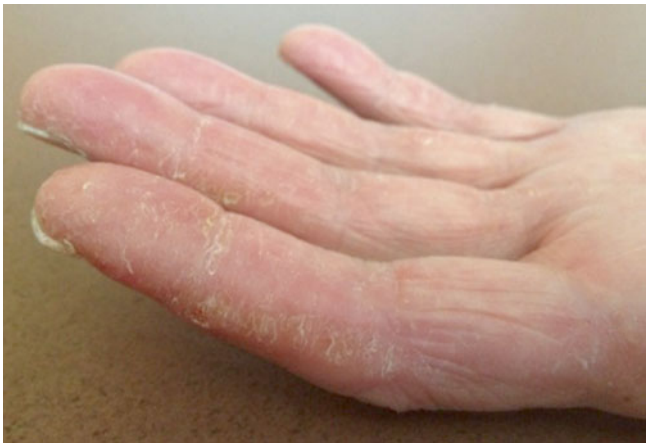

Fig. 27.3 "Mechanic's hands" (distal digital fissuring) in a patient with anti- synthetase syndrome

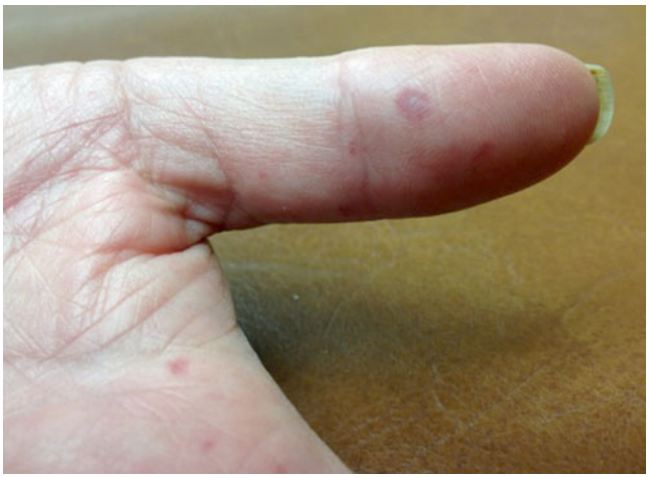

Fig. 27.4 Scattered palmar telangiectasia in a patient with systemic sclerosis sine scleroderma

Non-specific Symptoms Are Much Less Helpful

In contrast to the above examples, non-specific symptoms such as gastroesophageal reflux, pain, fatigue, dry eyes, dry mouth, alopecia, and weight loss are not helpful because they are ubiquitous symptoms encountered in the clinic and are not specific to CTD. Furthermore, their potential inclusion as criteria for determining presence of CTD is problematic because this will lead to over-diagnosis of CTD.

Autoantibodies (Table 27.5)

Autoantibody positivity is a hallmark of CTD and assessing for their presence is a fundamental component of an ILD evaluation. In the most recent guidelines for the diagnosis of IPF, a panel of screening serologies that includes ANA, RF, and anti-CCP antibody testing is recommended [36]. In addition to these autoantibodies, we would recommend a broader panel of screening serologies (Table 27.5). It is also important to take note of the pattern of immunofluorescence when the ANA is positive, as the nucleolar-staining ANA pattern in patients with ILD suggests SSc spectrum of disease [60].

Importantly, we highlight that the ANA and RF are poor screening tests: they have low specificity – particularly when present at low titer – and can be seen in healthy individuals. In addition, given that a negative ANA and RF may dissuade some clinicians from pursuing further evaluation, cases of occult CTD that may be ANA and RF negative (e.g. anti-synthetase syndrome) are missed. In fact, one might argue that by limiting screening serologies for occult CTD in "idiopathic" NSIP to ANA and RF alone will actually enrich this "idiopathic" cohort for the anti-synthetase syndrome because these individuals are characteristically ANA and RF negative!

High-Resolution Computed Tomography

Thoracic high resolution computed tomography (HRCT) imaging plays a central role in the evaluation of ILD by providing detailed information on the pattern, distribution and extent of the ILD, assessment of disease severity, and the presence of extra-parenchymal abnormalities including pleural disease and lymphadenopathy [61, 62]. Recent data show that certain extra-pulmonary findings on HRCT are suggestive of underlying CTD – and these include the presence of a dilated esophagus or pericardial thickening/effusion [63]. The most common chest imaging patterns are those that reflect the underlying pathologies of NSIP, UIP, organizing pneumonia (OP), diffuse alveolar damage (DAD) and lymphocytic interstitial pneumonia (LIP) [61–63]. Although there is a high degree of concordance between HRCT and lung biopsy for UIP pattern lung disease, HRCT is not as reliable when it comes to distinguishing cellular NSIP from fibrotic NSIP, identifying LIP, OP, or DAD, or evaluating for infection or malignancy.

Although HRCT images alone are not adequate to confer a label of CTD-ILD, the presence of certain suggestive features should heighten suspicions for underlying CTD:

The presence of bilateral, peripheral predominant ground-glass opacifications with reticulation and traction bronchiectasis suggests a pattern of fibrotic-NSIP and should raise strong suspicions for underlying SSc – particularly if significant dilation of the esophagus is noted (Fig. 27.5).

The combination of peripheral, lower lung-zone predominant ground-glass opacifications suggestive of NSIP in combination with dense consolidative opacification suggestive of OP should raise suspicions for the anti-synthetase syndrome – particularly when the pattern of lung injury hugs or "pancakes" the diaphragm [43] (Fig. 27.6).

The findings of thin-walled cysts diffusely scattered throughout the lung parenchyma should raise suspicions for LIP and associated Sjögren's syndrome (Fig. 27.7).

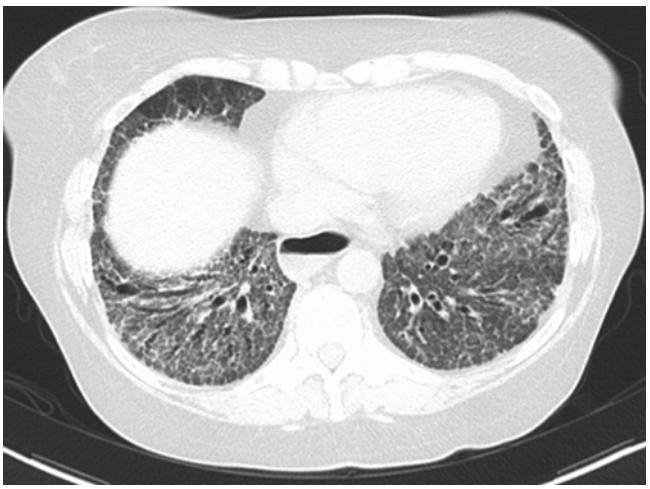

Fig. 27.5 High resolution computed tomographic image in a patient with systemic sclerosis demonstrating moderate bibasilar predominant ground glass opacifications, reticulation, traction bronchiectasis without honeycombing suggestive of fibrotic-NSIP. Note the markedly dilated, fluid-filled esophagus

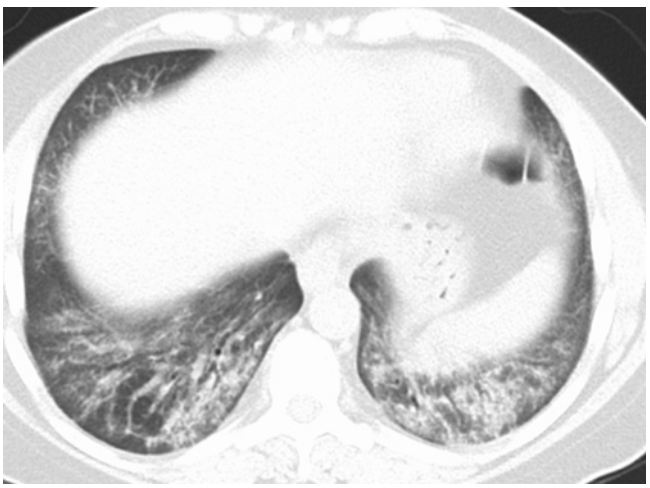

Fig. 27.6 High resolution computed tomographic image in a patient with the anti-synthetase syndrome demonstrating features suggestive of non-specific interstitial pneumonia in combination with overlapping organizing pneumonia. Note the extreme basilar distribution of the pattern of lung injury characteristic of this syndrome

Histopathology

Careful review of the histopathology from surgical lung biopsy specimens may provide clues that the ILD is a manifestation of underlying CTD [64]. There are a number of suggestive patterns and features observed on histopathology with known associations with CTD. A higher index of suspicion for CTD is warranted in any case of NSIP or LIP as these are two of the more commonly recognized patterns in patients with CTD. In addition, secondary histopathologic features that should raise strong suspicions for underlying CTD include the presence of dense perivascular collagen, extensive pleuritis, lymphoid aggregates with germinal center formation, and prominent plasmacytic infiltration [64]. Furthermore, a common feature of CTD-ILD is multi-compartment involvement; such that in addition to parenchymal disease, airways, pleural and vascular involvement are frequently identified [64]. These histologic features alert the pathologist that the injury pattern is suggestive of an underlying CTD.

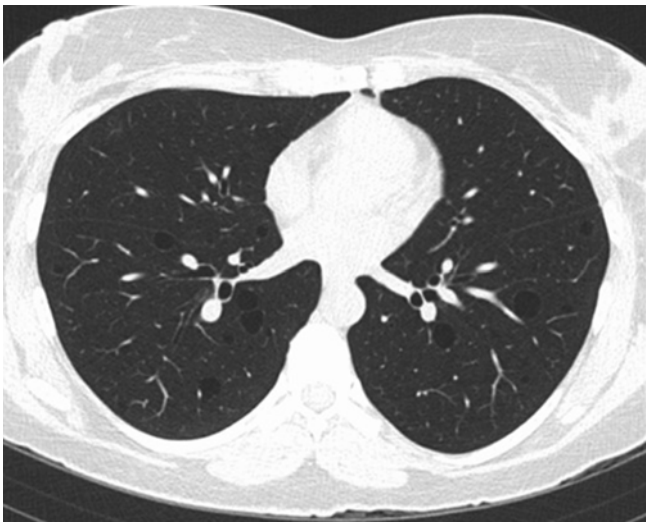

Fig. 27.7 High resolution computed tomographic image in a patient with Sjögren's syndrome demonstrating diffusely scattered thin walled cysts throughout the lung parenchyma suggestive of lymphoid interstitial pneumonia

Management Considerations

A general principle in CTD-ILD is that not all patients require pharmacologic treatment. As mentioned, subclinical ILD is commonly identified in patients with CTD, and only a subset of patients will show clinically significant, progressive disease [12]. The decision to treat CTD-ILD often rests upon whether the patient has respiratory impairment as a result of ILD, whether the ILD is progressive, and in consideration of any mitigating factors [4, 65]. Therapy for CTD-ILD is generally reserved for those patients with clinically-significant, progressive disease, and this determination is based upon a constellation of clinical assessment tools that include both subjective and objective measures of respiratory impairment [66]. The assessment of respiratory impairment in a patient with CTD should be comprehensive. Because CTD patients are often at high risk for pulmonary arterial hypertension, thromboembolic disease, and cardiovascular disease, determining whether respiratory symptomatology is due to ILD can be challenging.

When considering immunomodulatory therapy options for CTD-ILD, both pulmonary and extra-pulmonary disease

manifestations and degrees of activity need to be considered. The extra-pulmonary manifestations of a specific CTD often require immunosuppressive therapy yet the drug selected for the treatment of extra-pulmonary manifestations (such as inflammatory arthritis) may be one not typically employed for managing ILD (such as anti-TNFα agents) or may be an agent with significant potential for lung toxicity (such as methotrexate). In some cases the extra-pulmonary manifestations predominate, and as such, determine the choice of the initial immunomodulatory regimen.

In all cases of CTD-ILD, disease monitoring, choice of therapy and on-going longitudinal assessment and re-assessment of treatment response is complex. Efforts should be made to tailor any treatment recommendation to the individual, fully considering the numerous factors besides the ILD itself including the specific underlying CTD, medical co-morbidities, patient preferences and compliance, insurance coverage and access to care [65]. Unfortunately, we are left with few data to guide choice of specific therapeutic agents even for well-characterized forms of CTD-ILD. There are no data to guide therapeutic decisions for cases of undifferentiated forms of CTD-ILD, and as such, we can only borrow from our knowledge of therapies utilized in well-characterized CTD-ILD and IIP.

Corticosteroids (CS)

Because they have a rapid onset of action and anti-inflammatory properties, CS have served as an initial and mainstay of therapy for CTD-ILD. There are some small case series supporting the use of CS for CTD-ILD but no controlled studies [67–69]. We often incorporate knowledge of underlying histopathology when making treatment decisions, particularly as it relates to the use of CS. The more fibrotic forms of CTD-ILD are less CS responsive. Therefore, in cases of UIP or fibrotic NSIP, we use at most moderate doses of CS for relatively short periods of time. In contrast, in more cellular forms – particularly OP – we often implement high-dose CS for 4–6 weeks followed by slow taper along with initiation and titration of CS-sparing agents. One caveat to this strategy, based on data suggesting that SSc patients treated with moderate-high dose CS may be at increased risk of scleroderma renal crisis [70], is that one should consider limiting the daily prednisone dose to less than 15 mg per day for patients with SSc-ILD though this is determined on a case-by-case basis.

Cyclophosphamide (CYC)

CYC is one of the most potent steroid-sparing immunosuppressive medications employed for organ-threatening damage caused by CTD. The efficacy of CYC in the treatment of rheumatic diseases is based on controlled trials of patients with systemic vasculitis, lupus nephritis, and SSc-ILD [71– 75]. Retrospective studies have shown that in patients with progressive SSc-ILD, treatment with CYC is associated with improved pulmonary function and better survival [73, 74, 76]. Data from two recently completed controlled trials show that SSc-ILD patients treated with CYC for 12 months have improved quality of life, stabilization or modest improvement of pulmonary function, and less radiographic progression of fibrosis [71, 75, 77]. It appears that unless CYC therapy is continued beyond 12 months, or is followed by another effective immunosuppressive agent, the gains in pulmonary function attributed to the CYC treatment are lost over the following 12 months once therapy has been discontinued [77].

Mycophenolate Mofetil (MMF)

There are no controlled trials evaluating the efficacy of MMF for CTD-ILD. In 2006, Swigris and colleagues reviewed the effects of MMF for the treatment of 28 patients with CTD-ILD [78]. Over the course of therapy, the authors reported the daily prednisone dose decreased from 15 mg per day to 10 mg per day and that the percent predicted forced vital capacity (FVC) increased by 2.3 % and the percent predicted diffusing capacity for carbon monoxide (DLco) increased by 2.6 %. Moreover, the drug was well tolerated with a few side effects [78]. Similarly, Liossis and colleagues reported their experience with SSc-ILD in six patients, and found improvement in five of six patients both clinically and with objective testing [79]. More recently, additional centers published small case series further demonstrating that patients with CTD-ILD who were treated with MMF, had stable or improved lung function, and that the drug was again well tolerated [80–82]. In a recent abstract, Fischer and colleagues described the safety and tolerability of MMF in 125 subjects with a diverse spectrum of CTD-ILD treated with MMF for a median 897 days [83]. MMF was extremely well-tolerated and only discontinued in 13 patients (10 %). MMF was associated with significant improvements in estimated FVC% from initiation to 52, 104 and 156 weeks and in estimated DLco% from initiation to 52 and 104 weeks. In the subgroup without UIP-pattern injury, MMF significantly improved FVC% and DLco%, and in the subgroup with UIP-pattern injury, MMF was associated with stability in FVC% and DLco% [83]. Collectively, these data suggest MMF is a promising therapy for CTD-ILD and support the rationale of the ongoing Scleroderma Lung Study II, a randomized, blinded, multi-center trial of MMF vs. CYC in the treatment of SSc-ILD.

Azathioprine (AZA)

Controlled trials in RA, SLE, and other CTDs suggest that AZA is an effective steroid-sparing agent. In a recent placebo-controlled trial, Hoyles and colleagues demonstrated that in patients with SSc-ILD, administration of intravenous CYC for 6 monthly infusions followed by AZA may stabilize ILD [71]. In addition, isolated case reports, small case series and anecdotal experience suggest that AZA has some degree of efficacy for CTD-ILD [84, 85]. In one large trial of IPF patients, AZA plus CS plus NAC was shown to preserve lung function compared with CS plus AZA alone [86] but more recent data from the PANTHER trial suggest that the combination of AZA, prednisone and NAC may actually be harmful in patients with IPF [87]. It is not known whether any of these results can be extrapolated to CTD-associated UIP.

Cyclosporine and Tacrolimus

There are no controlled trials evaluating the efficacy of either agent in CTD-ILD. Controlled trials have demonstrated their effectiveness in the management of RA and anecdotal experience suggests that these agents are effective in other rheumatic diseases [88–90]. Interestingly, small case series suggest that cyclosporine and tacrolimus may be particularly effective in treating refractory PM/DM-associated ILD [91–93].

Methotrexate (MTX)

MTX is a first-line disease-modifying anti-rheumatic drug proved to be effective in the treatment of RA and numerous other CTDs. There are no controlled trials evaluating efficacy of MTX for CTD-ILD. Given potential acute pneumonitis associated with MTX and an overall reported incidence of pulmonary toxicity up to 5 % [94], we infrequently use MTX in patients with ILD as it may be impossible to discern between the development of MTX lung toxicity and progression of the ILD.

Biologic Agents

Over the past 15 years, the management of the rheumatic diseases has been revolutionized by the advent of targeted biologic therapy. In particular, the anti-TNFα antagonists have demonstrated high degree of efficacy for RA, inflammatory bowel disease, psoriasis, ankylosing spondylitis, and miscellaneous other auto-inflammatory diseases. However, the effect of these agents on ILD is not known. There have been numerous case reports describing the new development of ILD in patients being treated with each of these agents suggesting pulmonary toxicity [18, 28, 32, 95] as well as at least one report suggesting efficacy of anti-TNFα-therapy for RA-associated ILD [96]. It is noteworthy that in a controlled trial of IPF, etanercept was no more effective than placebo but without an excess number of adverse pulmonary events [97]. Though their role for the management of ILD in CTD patients is not known, the anti-TNFα class of drugs is commonly needed to control extra-pulmonary disease and the safe implementation of these agents routinely involves rheumatologic collaboration and expertise.

Complementary Modalities

Complementary modalities that are important to consider in any patient with ILD include: implementing a formal pulmonary rehabilitation or exercise program, ensuring appropriate use of supplemental oxygen, administering appropriate immunizations, instituting *Pneumocystis* prophylaxis, and addressing osteoporosis risks and treatment. Furthermore, screening and addressing common co-morbid conditions – especially cardiovascular disease, sleep apnea, gastroesophageal reflux disease, and pulmonary hypertension – are fundamental aspects of the longitudinal care of ILD patients in general, and particularly applicable to CTD-ILD.

Summary

The intersection of ILD and CTD is complex and commonly includes the scenario whereby ILD is the presenting manifestation of a well-characterized form of CTD or arises within the context of a poorly defined, undifferentiated form of CTD. There is much uncertainty and controversy surrounding these undifferentiated forms of CTD-ILD and there is far too little interdisciplinary dialogue in this arena. Having a consensus on how to best characterize and classify these individuals should lead to prospective studies that will yield a better understanding of the natural history of these cohorts, how to best manage them, and to help determine whether they truly behave as "CTD-ILD".

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Pulmonary Langerhans Cell Histiocytosis and Smoking-Related Interstitial Lung Diseases

28

Carlo Vancheri and Silvia Puglisi

Abbreviations

ACE	Angiotensin converting enzyme
AFIP	Armed forces institute of pathology
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DIP	Desquamative interstitial pneumonia
DLCO	Diffusing capacity for carbon monoxide
ERS	European Respiratory Society
FDG	Fluorodeoxyglucose
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
GM-CSF	Granulocyte macrophage colony stimulating factor
HRCT	High resolution computed tomography
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
LAM	Lymphangioleiomyomatosis
LCH	Langerhans' cell histiocytosis
LCs	Langerhans' cell
NSIP	Nonspecific interstitial pneumonia
PET	Positron emission tomography
PLCH	Pulmonary Langerhans' cell histiocytosis
RB	Respiratory bronchiolitis
RB-ILD	Respiratory bronchiolitis associated to interstitial lung disease
RM	Magnetic resonance
SR-ILD	Smoking-related interstitial lung disease
SUV	Standardized uptake value
TGF-β	Transforming growth factor-beta
TNF-α	Tumor necrosis factor-alpha
UIP	Usual interstitial pneumonia
VC	Vital capacity

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Introduction

Cigarette smoke contains a mixture of thousands of chemicals, many of which are toxic. This complex mixture of substances is the leading cause of preventable deaths, causing approximately 440,000 premature deaths in the United States annually [1]. The most common smoking related illnesses include chronic obstructive pulmonary disease (COPD), bronchogenic carcinoma and ischemic heart disease [2]. Only recently, cigarette smoking has been implicated as a major cause of interstitial lung diseases (ILDs). ILDs represent a heterogeneous group of lung disorders of known and unknown cause clinically characterized by cough and dyspnea, radiologically by the appearance of diffuse lung infiltrates and functionally by a restrictive pattern often accompanied by impaired gas exchange. Some ILDs such as respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) and desquamative interstitial pneumonia (DIP), although considered by the current ATS/ERS classification idiopathic forms [3], are thought to be related to cigarette smoking and thus also defined "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, significant epidemiological data have shown possible disease remission when smoking ceases [6]. In spite of that, the pathogenic mechanism explaining the correlation between these diseases and tobacco smoke exposure has not yet been 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 hypothesized

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that a small proportion of smokers may develop an excessive response to smoke, provoking interstitial and airspace inflammation as well as fibrous thickening of the alveoli. These events will eventually lead to the insurgence of symptoms such as cough and dyspnea and to impaired lung function. This condition, named RB-ILD, is related to smoking and is usually characterized by a good prognosis, with radiological and clinical resolution by simply stopping smoking, although some specific cases with severe clinical involvement may require corticosteroid therapy. Similarly to RB-ILD, DIP is characterized by macrophage accumulation in bronchioles and alveoli with the difference that the abnormalities are not only bronchiolocentric as in RB-ILD, but more diffuse. DIP usually has a worse prognosis if compared to RB-ILD, and it may require corticosteroid therapy, even though there are no specific studies evaluating its efficacy. PLCH is instead characterized in the earlier stages, by the presence of bronchiolocentric interstitial nodules whereas in more advanced stages, nodules start to cavitate and cysts become the predominant feature of the disease. PLCH may have a good prognosis if the patient stops smoking, even though a rapid clinical deterioration may sometimes require the use of chemotherapeutic agents. Although SR-ILDs may have distinctive histopathological and radiological features, mixed patterns of SR-ILDs may frequently coexist in the same patient, making diagnosis difficult and supporting the concept that RB-ILD, DIP and PLCH form a spectrum of interstitial patterns of lung injury related to cigarette smoke [7]. However, the predominant idea is to consider these diseases as different entities linked by a common etiologic factor: cigarette smoke.

Recently, acute eosinophilic pneumonia (AEP) has also been included in the SR-ILD group after an outbreak of the disease among US military personnel deployed in Iraq. It has been hypothesized that smoking may precipitate this acute entity in young adults with a recent onset of heavy tobacco use. Acute eosinophilic pneumonia (AEP) is considered a rare disorder and few cases of AEP have been reported in 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, and pulmonary eosinophilia. AEP mimics pulmonary edema on chest radiographs, reticular opacities and interlobular septal thickening are present in the earlier stages of the disease. On HRCT scans interlobular septal thickening and patchy ground glass is frequent, and consolidation areas 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 smoker whereas in IPF the prevalence of smokers or former smokers varied 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 consider these three conditions in the list of entities having cigarette smoke as their common etiologic factor.

Pulmonary Langerhans' Cell Histiocytosis

Introduction

Histiocytic disorders are rare diseases characterized by abnormal infiltration of certain organs by "histiocytes"; this term is referred to a group of immune cells that includes macrophages and dendritic cells. Langerhans' cells (LCs) belong to the family of dendritic cells, but can be distinguished from other cells in this lineage by their tissue location, morphological features and properties [10]. A medical student, Paul Langerhans, during his studies about tactile corpuscles in human skin was the first to describe these cells in 1868 [11]. Almost 100 years after Langerhans' original observations, LCs have been 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, exophthalmus, and diabetes insipidus, Letterer-Siwe disease, a multiorgan disease of children affecting liver, spleen, lymph nodes, lungs, and bones and eosinophilic granuloma defined as a solitary or multiple histiocytosis 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, including eosinophilic granuloma, Letterer-Siwe disease, Hand-Schuller-Christian syndrome, Hashimoto Pritzker syndrome, self-healing histiocytosis, pure cutaneous histiocytosis, Langerhans' cell granulomatosis, Langerhans' cell granulomatosis, type II histiocytosis, and non-lipid reticuloendotheliosis. Eventually, in 1987, the Histiocyte Society endorsed the term "Langerhans cell histiocytosis" to replace the term histiocytosis X and 10 years later presented a new classification of histiocytic disorders divided into groups according to organ involvement. The new classification of histiocytic disorders was also possible thanks to the advent of high-resolution computed tomography (HRCT) that improved imaging and characterization of histiocytic lesions. Depending on the organs involved, LCHs were 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 instead, is further subdivided into low risk and risk patients, 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 affecting adults, was categorized as an LCH variant, different from the severe and lethal pulmonary involvement seen in multisystem disease [14, 15].

Epidemiology

Precise data regarding the prevalence of PLCH are not available. In a 5-year prospective study in 20 pulmonology centers in Belgium, 360 patients with interstitial pneumonia were identified, of whom 3 % had PLCH [16]. 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 [17]. A large epidemiological study was conduced 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 LCH diagnosis: 31.4 % (86 patients) were single-system LCH, including isolated pulmonary involvement in 44 patients; 68.6 % (188 patients) had instead a multisystem disease [14]. A study of discharge diagnoses, realized in Japan, in 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 population in males and females, respectively [18]. Though the widespread use of HRCT is helping to discover new cases of PLCH, the prevalence of the disease is probably still underestimated because some patients are asymptomatic, experience spontaneous remission or their histological findings are not specific for PLCH. No accurate epidemiological data are available regarding racial differences [15]. PLCH predominantly affects young adults, with a frequency peak at 20–40 years of age [19]. A marked male predominance was initially reported, however, more recent studies show a similar proportion of males and females, or even a slight predominance of females, particularly in series from the USA. These differences probably reflect smoking habits over time. A particular finding in epidemiological data, is the difference between isolated PLCH incidence in children and adults. Isolated PLCH is less frequent in children than multisystem disease suggesting it is a different form of PLCH with no correlation to cigarette smoke. More convincing are the data supporting a causal relationship between cigarette smoke and PLCH in adults. Many studies have in fact shown that more than 90 % of adult patients who develop PLCH smoke cigarettes 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 [15, 20]. In current smokers cigarette smoke induces macrophage recruitment and accumulation around small airways, interstitium and distal airspace 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 possible to hypothesize that smokers with PLCH develop 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 have a role in promoting smoking-induced PLCH and continues to be an important area for future investigation [21]. A direct effect of tobacco smoke, however, fails to explain the occurrence of PLCH in adult nonsmokers.

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 the disease results from a neoplastic process or is reactive to, as yet unidentified, stimuli. According to Wilman et al., LCH has been shown to be a monoclonal proliferation of histiocytes, supporting a neoplastic origin [22]. However, another study suggests polyclonal expansion of LCs in the lungs of patients with PLCH. Yousem et al. [23] 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) locus was used to assess clonality in female patients undergoing lung biopsy. LCs from pulmonary nodules were studied for differential methylation patterns at the HUMARA locus: 29 % were clonal and 71 % were non-clonal. Thus, it can be supposed 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 [21]. 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 towards 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 over-expressed 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 [21]. Granulocyte macrophage colony stimulating factor (GM-CSF) is another cytokine produced by epithelial cells and fibroblasts playing an important role in 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 [24]. 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 who spontaneously produce increased amounts of osteopontin. Osteopontin is a glycoprotein involved in cell-mediate 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, in healthy smokers very low osteopontin levels were observed and completely no production in healthy nonsmokers volunteers, suggesting that an increase in osteopontin production is not common to all inflammatory lung diseases but is instead an indicator of a special type of macrophage activation due to cigarette smoke. Cigarette smoke constituents may in fact stimulate the epithelium, increase the production of proinflammatory cytokines, including osteopontin, so inducing the recruitment of alveolar macrophages and the differentiation of LCs. It is still unexplained the different concentration of cytokines and osteopontin in BAL cells from DIP-PLCH patients and healthy smokers [25]. 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, and suggest that cigarette smoke may directly promote pro-survival dendritic/LCs pathways [21].

Clinical Vignette

A 18-year-old woman with a 2 years history of tobacco smoking, went to her doctor complaining for chest pain. The patient was previously healthy and was not taking regular medication of any kind. After a chest radiography showing the presence of a spontaneous right pneumothorax, an HRCT also revealed evidence of nodules, some of which cavitated, and initial lung cysts extended throughout the lungs sparing only the costo-phrenic angles (Fig. 28.7a–c). Pulmonary function tests, performed at the diagnosis, showed normal spirometric values, normal walking test and a decreased DLCO value (56 %). A bronchoscopy with BAL was performed showing the presence of CD1 to be equal to 8 %. Nevertheless, a lung biopsy was performed and the histological diagnosis was compatible with PLCH. CD1 and S100 positive cells were found. No extra-pulmonary manifestations of the disease were found. The patient quit smoking soon after the definitive diagnosis was made. The patient was monitored closely with regular 3-monthly follow-ups that showed a substantial stability of the disease. Thanks to the frequent follow-up, it was possible to identify a clinical-radiological and functional decline of the disease 1 year after the diagnosis. On CT scans many new cysts were found, some formed by the confluence of smaller cysts. The biggest cysts were up to 6–7 cm of diameter, with a parenchimal loss of 30 % in 1 year. The patient, for the first time, complained of dyspnoea on exertion and coughing. Considering the progression of the disease and the patient's young age, a therapeutic approach was started. In line with the Histiocyte Society study the patient was treated with prednisolone + vinblastine + 6mercaptopurine for 6 months. Since completion of the therapy a functional and clinical improvement has been observed. Symptoms gradually disappeared and DLCO increased to 70 %. Six years after therapy lung function is back to normal and symptoms are absent.

Clinical Features

Establishing a diagnosis of PLCH requires a high index of clinical suspicion. Physical examination findings and laboratory tests are generally non-specific 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 [26]. 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 [27]. The occurrence of pneu-

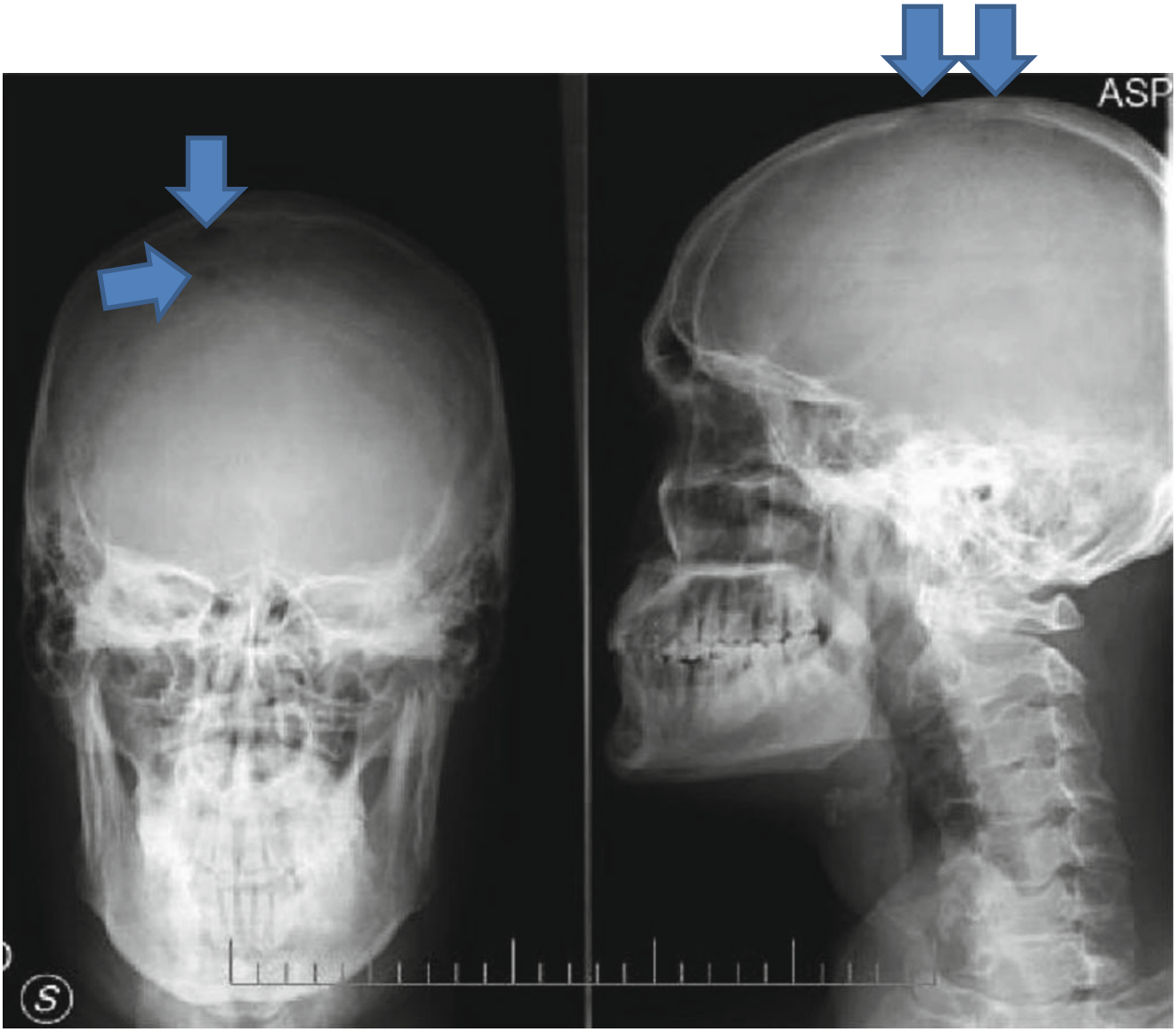

Fig. 28.1 Skull X-ray of a patient affected by PLCH. It shows two little osteolytic bone lesions easier to recognize in the lateral skull radiograph

mothorax is more common in young males, occurs at any time during the course of the disease, may be bilateral, recurrent and constitutes a difficult therapeutic challenge [15]. Hemoptysis is uncommon and should not be attributed to PLCH until other causes such as bronchogenic carcinoma or development of aspergilloma in 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 [21].

Even if PLCH in adults is usually a single-system disease, in 10–15 % of adults with PLCH, symptoms provoked by extra-pulmonary disease may be present. 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 extra-pulmonary manifestations (Fig. 28.1) [15]. Islinger et al. reviewed a series of LCH patients with bone lesions evaluated by AFIP 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 possible localizations of bone lesions can be found in long bones and mandible [28]. The radiological appearance of bone lesions and clinical manifestations depend 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 have 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 and increase in number and extension. Osseous perforation may evolve downwards into epidural

or epicranial soft tissue mass. 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 with the radiological appearance of "floating teeth". Rib involvement is demonstrated by osteolysis area, periostitis and fracture. Sometimes it is possible to find an extrapleural mass resulting from soft tissue extension, which causes pain. Pelvis involvement is characterized by poorly defined areas of osteolysis that with time will be characterized by a well-defined scleroting margin. 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 are different and based on observation, surgical intervention such as curettage or total excision, radiotherapy and chemotherapy. Although option treatments for adults have never been clarified by a clinical trial, studies are present in literature comparing the efficacy of different chemotherapy treatments. Recently Cantu et al. studied 58 adult LCH patients with bone lesions constituting either the only site or 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 [29].

Another important extrapulmonary complication is pulmonary hypertension. It is more severe in PLCH than in other interstitial lung diseases and histopathologically it is possible to recognize intimal fibrosis and remodeling of both venous and arterial systems [30]. Dauriat et al. estimated pulmonary hypertension in 92 % of 36 patients evaluated for lung transplantation [31]. Pulmonary hypertension is associated to poor prognosis so that it is necessary to screen all patients, especially those with excessive dyspnea and normal lung function tests, looking for ecocardiographic signs of pulmonary hypertension [30]. In selected cases cardiac catheterization would be necessary to confirm the diagnosis. When the diagnosis is made, therapy with vasodilators including phosphodiesterase inhibitors or endothelin receptor antagonists may be useful with an objective reduction in pulmonary artery pressure and improved exercise capacity. However, their potential capacity to worsen arterial oxygenation as a result of a greater imbalance in ventilation/perfusion must also be considered. This is possible because drugs can inhibit hypoxic pulmonary vasoconstriction. Le Pavec et al. reported their experience in a group of 29 PH-PLCH patients treated with the usual pulmonary hypertension therapies: endothelin receptor antagonist, phosphodiesterase 5 inhibitor and iloprost. Patients showed improvement in hemodynamics without oxygen worsening or pulmonary edema. However more studies are needed to evaluate safety and efficacy of usual pulmonary hypertension treatments in PH-PLCH [32]. Supplemental oxygen may be useful to correct hypoxemia while prostacyclin can cause severe pulmonary edema and should be used very cautiously in these patients because of the venous involvement.

Central nervous system (CNS) complications may occur in 1–11 % of LCH patients and can be subdivided clinically into two groups: the "neurodegenerative like" form which is characterized by neural cell loss and pyramidal syndrome; and the "mass lesion" form presenting as a space occupying lesion that may appear anywhere in the CNS. Very few studies are present in 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 aggressive form of LCH, in patients with CNS mass lesion with a response rate of up to 70 %, while no effect has been described on neurodegenerative lesions [33].

Pulmonary Function Tests

Pulmonary function test findings are variable and the disease can be associated to a restrictive, obstructive or mixed pattern depending upon the course of the disease and prevalent anatomical lesions. In literature there are contrasting studies. According to Tazi et al. the obstructive pattern is the most frequent and there is evidence that flow–volume curve alterations are present in 50 % of patients, with the ratio of forced expiratory volume in 1 s (FEV1) to vital capacity (VC) diminished in 20–30 % of patients with recent onset of PLCH. This pattern may be related to the bronchial involvement characteristic of smokers, or to bronchiolar obstruction due to peribronchiolar fibrosis or inflammatory infiltrates [15]. On the contrary, Crausman et al. described a restrictive pattern in 11 patients of a cohort of 23 patients with early PLCH diagnosis. However, in advanced stages a restrictive pattern is usually the predominant pattern because of extensive lung fibrosis [21, 34]. At the time of diagnosis up to 20 % of patients may also have normal pulmonary function tests while, approximately 60–90 % of patients have low diffusing capacity for carbon monoxide (DLCO). Blood gas level at rest stay usually normal for a long time although it is possible to discover hypoxemia, and exercise limitation even in the earlier disease [15]. Canuet et al. tried to correlate lung function with HRCT lesions showing that the extent of cysts, is closely associated with the impairment of both lung function and gas exchange. A predominantly nodular pattern, suggestive of an active inflammatory disease, has instead only moderate functional consequences [35].

Tazi el al similarly described the correlation between lung function and HRCT lesions. They studied a group of 49 PLCH patients who experience a deterioration of lung function in 60 % of cases with a decline of FEV1 in 40 % of patients and a decline of DLCO in 50 % of the patients. The DLCO was reduced in some patients suggesting the hypothesis of pulmonary hypertension. However, according to other studies in literature the main pattern of lung function defect was represented by airway obstruction and this finding is consistent with the bronchiolar localization of pulmonary

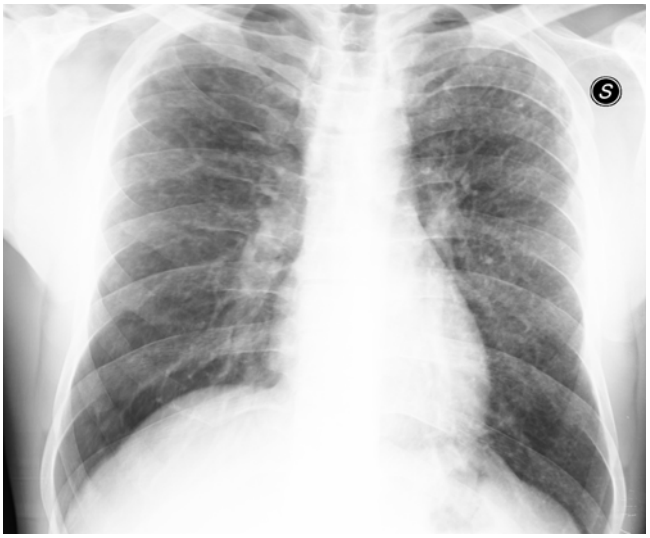

Fig. 28.2 Chest X-ray in a patient affected by PLCH. Small and poorly defined nodules are predominantly distributed in the upper and middle lung zones with the characteristic lower zones sparing

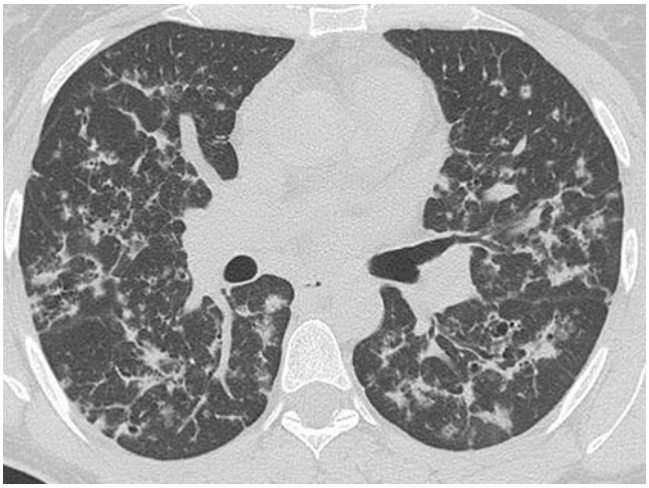

Fig. 28.3 HRCT of the lungs of a patient affected by PLCH, showing a predominant nodular pattern. It is possible to describe centrilobular and peribronchiolar nodules, some of which are cavitated (Courtesy of Professor N. Sverzellati. University of Parma, Italy)

LCH lesions. The extension of cysts on HRCT scans correlated with a deterioration in lung function parameters so that serial lung function tests can be useful during follow-up, while routine serial HCRT seem to be less useful and expose these young patients to the dangers of radiation [36].

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 are present as single or merging nodules. The distribution of nodules is limited to upper/middle lung zones with sparing of the lung bases near the costophrenic sulci (Fig. 28.2). As the disease progresses, reticular-nodular abnormalities and cystic changes may predominate. As cysts become more numerous, nodules tend to occur less frequently [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 radiographically indistinguishable from advanced emphysema or LAM. Especially in end-stage PLCH it is possible to find increased lung volumes on chest radiography and this can help to distinguish PLCH from other interstitial lung diseases which are instead characterized by reduced lung volumes (with LAM exception). Pneumothorax is known to be a complication of PLCH and may occur in the absence of other radiographic pulmonary abnormalities. Altogether, 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 normal. A rare finding in PLCH chest radiography is a solitary pulmonary nodule as described by Khoor et al. in a 45-year-old male cigarette smoker. Biopsy was performed to establish the nature of the nodule that showed the histologic and immunophenotypic characteristics of PLCH. Twenty-one years after its excision, appeared a new contralateral lung nodule which remained unchanged during 36 months of observation. Other rare finding in PLCH is represented by pulmonary artery prominence, due to pulmonary hypertension that may occasionally complicate PLCH [37].

High Resolution Computed Tomography (HRCT)

HRCT is superior to radiography in demonstrating the morphology and distribution of lung abnormalities. Presentation patterns differ according to the stage of PLCH. In the early stages of the disease, as described by Brauner et al., a nodular pattern is usually recognizable, defined by the presence of multiple nodular opacities measuring 1–5 mm in diameter or larger [38]. Nodule sizes are usually less than 10 mm in diameter as also shown by Grenier et al. who observed nodules under 10 mm in diameter in the majority of CT scans from PLCH patients [39]. These small nodules, usually underestimated on chest X-rays, are characterized by irregular margins and are surrounded by normal lung parenchyma (Fig. 28.3). They may be profuse and are generally solid, although cavitation may occur with time. However, the predominant characteristic of lung nodules is their distribution. There is a topographic predominance in the upper and middle lung zones with relative sparing of the lung bases and

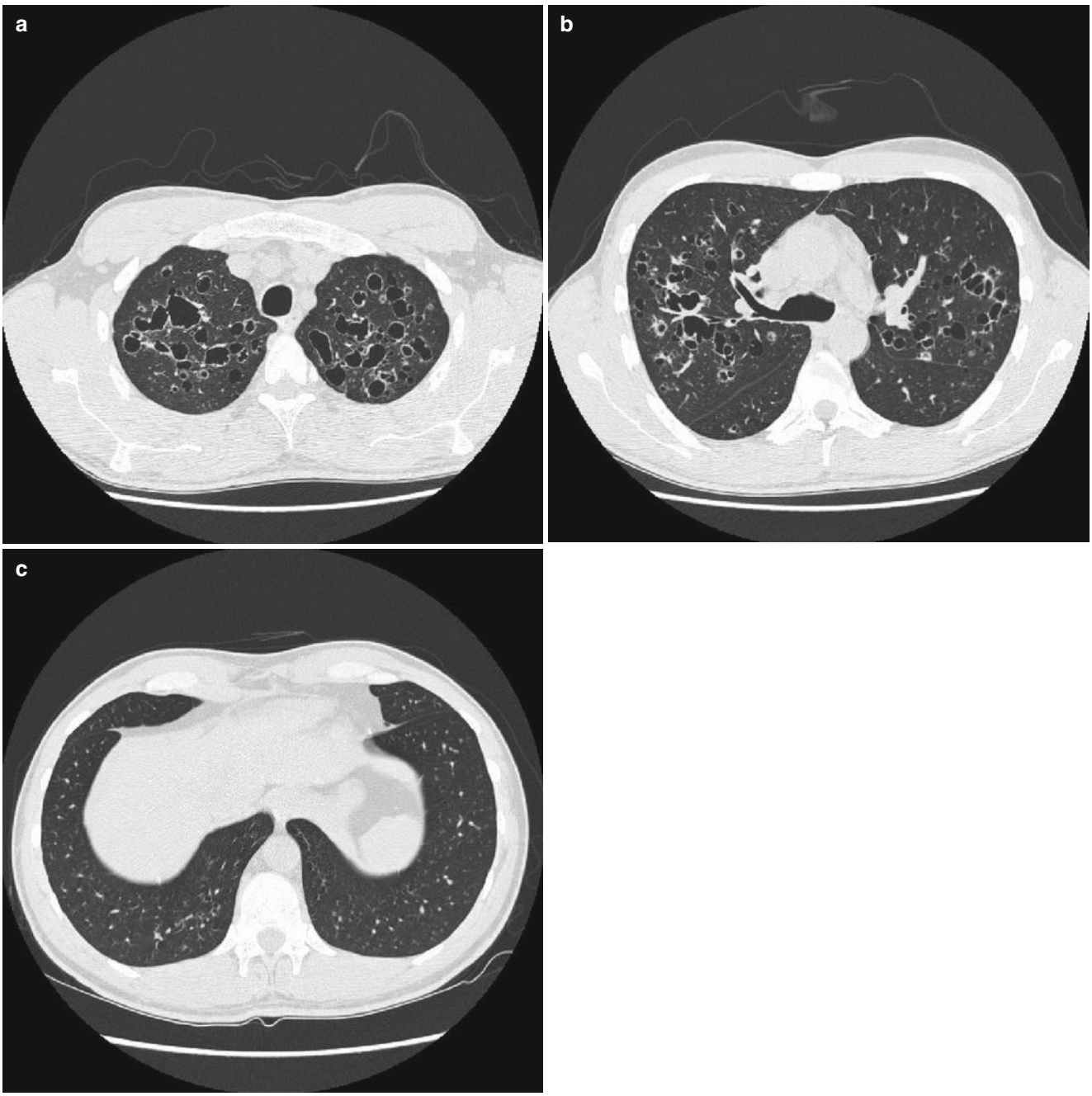

Fig. 28.4 HRCT of the lungs of a patient affected by PLCH showing a predominant cystic pattern. The cysts are characterized by variable wall thickness and bizarre shapes (**a**). It is possible to identify centrilobular and bronchiolocentric nodules, some of which start to cavitate (**b**). Note the predominant upper lung involvement with relative sparing of the lung bases (**c**)

most nodules show a centrilobular or peribronchial distribution, reflecting the bronchiole-centered development of PLCH lesions. According to Brauner et al. a temporary progression of these pulmonary nodules into cavitary nodules and then into cysts is possible [38]. In point of fact, follow-up scans showed a decreasing preponderance of nodules and an increasing number of thin-walled cysts. Cystic lesions tend to be initially small, with diameters of less than 10 mm, and thick-walled; then they become bigger with diameters up to 20 mm and thin-walled. Cyst formation progresses from cavitation within a centrilobular nodular lesion through an increasing bronchiolar dilatation resulting from granulomas destruction and supervening fibrosis on the edges of the lesion. Cyst distribution is also prevalent in upper lung zones where they can appear as round or ovoid cystic spaces or with bizarre shapes that may result from coalescence of adjacent cysts (Fig. 28.4a–c). Some of these cystic spaces may attain bulla sizes of up to 80 mm. Advanced

disease is characterized by substantial architectural distortion due to cysts with few nodules [40] 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, indicating that nodules may be reversible, while cystic lesions remain unchanged or worsen with time [41]. There remains the question of whether a relationship exists between HRCT lesions and histopathological abnormalities. Soler et al. compared the nature of the main lesions on CT scans with that of lesions presented on biopsy samples in PLCH patients. They found that the usual, early-stage PLCH histopathological lesion consisted of florid granulomas that were mainly composed of typical LCs associated with macrophages and inflammatory cells, particularly lymphocytes and eosinophils. Interestingly, all patients showing a predominant nodular pattern on CT scans had florid granulomas in their lung tissue. In more advanced disease, cavitary 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 this case few cavitated nodules or thin-walled cysts were seen in CT scans. In late-stage PLCH fibrous cysts of variable size, demarcated by a fibrous ring of variable thickness, containing no LCs and few or no inflammatory cells are usually found [42]. 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 (10 patients) corresponding to peribronchiolar granulomas with LCs on biopsy. Nodules were typically present on upper lung zones with a random distribution. Thick, thin walled-cysts and bizarre shape cysts were respectively present in 4, 8 and 5 patients with a central cavity surrounded by a thin wall of LCs and eosinophils with a random distribution in the upper lung zones. Cystic lesions independently by the shape, can correspond to cavitated granulomas or to fibrous cysts. These two studies suggest that while it is possible to conclude that a nodular pattern on CT scans reflects a histopathologically active PLCH disease, no correlation is possible between histological and radiological findings in the case of patients with a cystic pattern because HRCT cannot differentiate between fibrous cysts and cavitary granulomas [41]. Canuet et al. tried to correlate lung function with HRCT lesions and showed that the distribution of cysts, was closely associated with an impairment of both lung function and gas exchange. A predominant nodular pattern, suggestive of an active inflammatory disease, has only moderate functional consequences and it was not significantly correlated with lung function parameters. A predominant cystic pattern was instead strongly correlated with lung function parameters [35]. Nodular changes may be present in several other lung diseases including sarcoidosis, silicosis, tuberculosis, RB-ILD, hypersensitivity pneumonitis or metastatic disease [42]. In some of these cases the radiologic differential diagnosis with PLCH may turn into a dilemma. All these conditions are in fact characterized by a centrilobular nodular pattern of presentation on CT scans. However, the nodule distribution is one aid to a correct diagnosis. Perilymphatic distribution is typical of sarcoidosis in which nodules are predominantly present in interlobular septa, peribronchovascular and sub-pleuric spaces. Random distribution of nodules is possible in miliary tuberculosis and hematogenous metastases and it is characterized by a random location of the nodules in the secondary pulmonary lobule. In some cases it can be difficult to differentiate metastatic nodules from PLCH nodules although metastatic nodules are often surrounded by a halo of ground glass attenuation useful to make the differential diagnosis. In other cases only lung biopsy may have a discriminative importance [43]. When only cysts are seen on the CT scan, a differential diagnosis has to be made between PLCH and other lung diseases with a cystic CT-scan pattern such as idiophatic pulmonary fibrosis (IPF), emphysema, bronchiectasis and lymphangioleiomyomatosis (LAM). Differential diagnosis between IPF and PLCH is necessary when CT scans indicate honeycombing, defined as the presence of air-filled cystic spaces that often predominate in a peripheral sub-pleural location. These cysts can be of different sizes with a wall thickness between 1 and 3 mm, consisting of fibrous tissue lined by bronchiolar epithelium, which is shared by adjacent cysts. This is specific for honeycombing and not seen in cysts that are found in PLCH. However, a differential diagnosis can be easier because honeycombing is often associated with other findings of pulmonary fibrosis such as reticular opacities, irregular sub-pleural 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 lower zones sparing, typical of PLCH, while IPF is characterized by bi-basal and sub-pleural distribution of the cysts with the typical apical-basis gradient. 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 emphysema by the focal areas of low attenuation that are found in PLCH, contrasted by surrounding normal lung, and by the absence of walls [44]. Bronchiectasies are localized, irreversible bronchial dilatation, very often with thickening of the bronchial wall that may be mistaken for cystic airspace disease when a dilated airway is viewed "frontally". 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 [45]. LAM is characterized on CT scans by the presence of thin-walled cysts of variable size from 2 to 40 mm diameter. 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 uniformly all regions of the lungs without sparing the costo-phrenic angles [45, 46].

Bronchoscopy and Bronchoalveolar Lavage (BAL)

Bronchoscopy is a well tolerated procedure that can provide further information for the correct diagnosis of PLCH. In PLCH the bronchial tree is usually either normal on gross examination or there are signs of non-specific inflammation due to smoking. It is possible to identify different nonspecific features in the bronchoalveolar lavage fluid of PLCH patients, such as 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 typically present in the BAL fluid of smokers where there is no evidence of interstitial lung disease, so it is necessary to look for other disease markers in the BAL fluid. 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 [47]. 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 so 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 it is possible to fix a threshold of 5 % LCs to define the test as specific, although the sensitivity remains quite low (<25 %) [15]. Smetana et al. demonstrated the presence of another cell marker in the BAL fluid of PLCH patients named Langerin (CD207). This is a protein 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. This analysis showed that the numbers of CD1a and Langerin positive cells were almost identical in all the tested cases, underlying the potential relevance of Langerin in improving the usefulness of BAL in the diagnosis of PLCH [49], although its real diagnostic utility has yet to be assessed in clinical studies. Bronchoalveolar lavage rarely establishes a definitive diagnosis of PLCH in adults, despite this, it is helpful in the differential diagnosis of infectious diseases characterized by the presence of excavated nodules, such as Pneumocystis jiroveci pneumonia, or in patients without a typical radiological pattern where it can orientate towards the diagnosis to PLCH showing high alveolar macrophage counts or increased levels of LCs.

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 [50]. However, transbronchial lung biopsy remains useful for differential diagnosis by excluding other disorders, such as sarcoidosis. Even if 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 relies on pulmonary biopsy. In those cases where 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 surgical risk [15]. In a patient with suspected PLCH and an extra-pulmonary lesion with compatible HRCT findings, a diagnosis may be provided by a biopsy of this lesion. However, the majority of adults have isolated PLCH, which makes a surgical lung biopsy using video-assisted thoracoscopy or open thoracotomy useful for a correct diagnosis. Since the lesions are focal the specimens should be sufficiently large to take an adequate quantity of material, preferably from different areas of the lung. Lung biopsy can generally be avoided when HRCT findings are characteristic and concordant with the clinical history [42].

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 are seen as focal lesions with irregular and stellate borders. In advanced disease phase, the predominant finding is a hyperinflated lung with cysts and honeycombing formation [42]. On microscopic examination, the characteristic early lesions in PLCH are situated in terminal and respiratory bronchioles and are formed by activated LCs organized into a loose granuloma associated with lymphocytes and inflammatory cells like eosinophils and macrophages (Fig. 28.5a, b) [10]. The morphology of LCs found in these inflammatory nodular lesions is generally similar to that of LCs in normal tissues: they are of medium size with elongated nuclei, 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 CD1 (Fig. 28.6) or by the recognition of Birbeck granules, identifiable through electron microscopic visualization. Birbeck

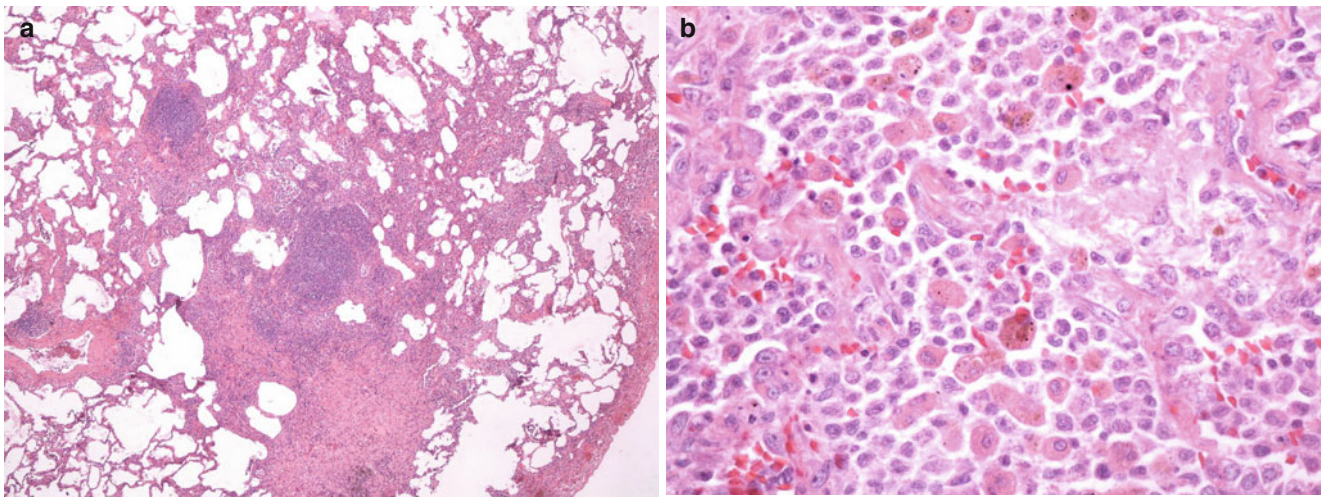

Fig. 28.5 LCH with centrolobular nodules with irregular margins (**a**) and aggregates of Langerhans cells together with "golden" macrophages and eosinophils (**b**) (Courtesy of Professor G. Rossi. University of Modena-Reggio Emilia, Italy)

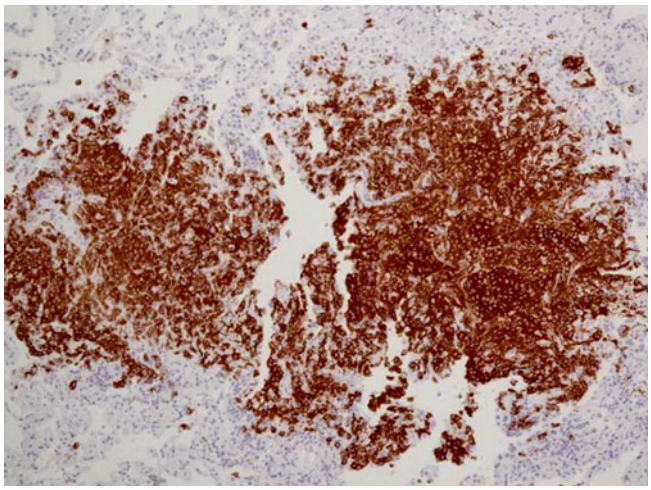

Fig. 28.6 CD1a further highlights Langerhans cells at immunohistochemistry (Courtesy of Professor G. Rossi. University of Modena-Reggio Emilia, Italy)

granules are intracytoplasmic organells 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, separated by apparently normal lung parenchyma, and centered on the terminal and respiratory bronchioles destroying the airway walls, thus giving the impression that PLCH mimics bronchiolitis rather than being a diffuse infiltrating 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 that results from the residual lumen of the bronchiole destroyed by granulomatous reaction and not from its necrosis. The 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 granuloma. 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 giving the characteristic aspect (Fig. 28.4). 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 [15].

Diagnosis

When PLCH is suspected on the basis of clinical-radiological and anamnestic features it is necessary to continue searching for other organ involvement of the disease. Skeletal X rays are necessary to investigate the presence of bone lesions, serological investigations to evidence increased plasma osmolarity and RM of the brain can be helpful to identify possible involvement of hypothalamic region.

Treatment Options

The recruitment of a sufficient number of patients for controlled therapeutic trials has been hampered by the low incidence of PLCH and its 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 sug-

gests that cigarette smoke plays a role in the pathogenesis of the disease. Therefore, it is necessary that patients stop smoking and this should be encouraged, especially in heavy smokers, through smoking cessation programs [15]. Some case reports have shown that this alone 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 a functional improvement with DLCO increase [20]. Similarly, Negrin-Dastis [51] described a PLCH case with total regression of radiological lesions after 12 years of smoking cessation. Because of the rare incidence of PLCH and the unpredictable course of the disease, there are no reliable data regarding the efficacy of smoking cessation on disease resolution as showed by Tazi et al. [52] who reported four PLCH cases with biopsy proven PLCH diagnosis: all of them were smokers and their disease initially underwent regression just by smoking cessation and subsequently developed reactivation with the appearance of new nodules on CT scans, thus requiring corticosteroid therapy. However, other studies provide contrasting data, describing cases where the disease has worsened despite smoking cessation [52, 53] and recently Tazi et al. have described how smoking cessation did not modify the pulmonary LCH outcomes in a group of 49 LCH adult patients [36]. This leads us to conclude that smoking cessation might lead to an improvement in the clinical and radiographic findings or even to the resolution of the disease but it should also be remembered that the disease can improve by virtue of its natural course 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 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 while in advanced stages the presence of fibrosis may explain a lack of response to therapy. On this basis, it has been suggested that initiating corticosteroid therapy in symptomatic PLCH with a predominant nodular pattern on HRCT scans can improve radiological and clinical features. Usually prednisone or prednisolone are administered at a starting dose of 0.5–1 mg/kg/day tapered over 6–12 months [15]. 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 [54]. In case of disease progression in spite of a 6-month period of steroid treatment, the disease can be treated with chemotherapy. The agents used 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 made possible to start new trials. Different perspective randomized trials were 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 assumed vinblastine (6 mg/m^2) intravenously every week, or etoposide (150 mg/m^2/day) intravenously for 3 days every 3 weeks and a single initial dose of corticosteroids. There was no difference in survival or disease reactivation rates but the absence of response after 6 weeks of treatment was 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 three 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 per day, 1-h infusion weekly for 6 weeks). At the 6th week, the continuation therapy was 6-mercaptopurine (50 mg/m^2 daily orally) and pulses of oral prednisone (40 mg/m^2 daily in three doses, days 1–5) and vinblastine (6 mg/m^2 per day once every 3 weeks) in the first group, while the second group added vinblastine every 3 weeks. The total duration of treatment was 24 weeks. This trial showed that more intensive treatment increases response rates and reduces mortality from LCH [55]. The Histiocyte Society has recently closed its third clinical trial conduced 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 a pediatric population, 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 [56]. In multisystem LCH, often refractory to treatment and characterized by frequent relapse, there is no current 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 [57]. 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's lymphoma and consists of a combination of prednisolone, vincristine, bleomycin, metotrexate, doxorubicin and ciclophosphamide. A 100 % response rate in all seven adult patients was reported [58].

However PLCH treatment is not standardized, and data regarding the effectiveness of treatment are derived from observational studies, case reports and expert opinion. More studies are needed regarding less toxic and more effective treatments.

Another important treatment to be considered is pleurodesis in cases of recurrent pneumothorax following the rupture of a cystic lesion. Mendez et al., demonstrated the superiority of pleurodesis to tube thoracostomy alone in ipsilateral recurrence of pneumothorax [59].

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 and observed resolution in five of these patients while the other two patients have suffered recurrence of LCH in the grafted lung. These two patients resumed smoking after transplantation and had extrapulmonary localization of the disease [60]. A retrospective multicenter study on 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 the extrapulmonary disease before transplantation and a resumption of smoking have been described as risk factors for recurrent disease so that, although lung transplantation may be an efficient treatment for end stage LCH, the risk of recurrence must be considered [31].

Course and Prognosis

PLCH is characterized by an unpredictable course 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. Identification of patients with poor prognosis could be useful in deciding who will benefit from aggressive treatment early in the course of disease. According to Delobbe et al., older age, lower FEV1/FVC ratio at diagnosis and prolonged corticosteroid therapy suggest an adverse prognosis [61]. 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 [62]. In a more recent study Vassallo et al. studied a cohort of 102 PLCH patients and the median survival was estimated to be of 12.5 years showing that adult patients affected by PLCH have a shorter survival than general population. Reduced DLCO or severe COPD due to concomitant cigarette smoke were considered as possible negative prognostic factors [50]. Pulmonary hypertension is an unrecognized complication of PLCH that is related to poor prognosis [63]. 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 it would be useful to confirm and define the severity of pulmonary hypertension [21]. Multiorgan involvement may be characterized by poor prognosis and for correct management of PLCH is necessary to investigate other possible organ 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 have been demonstrated in other conditions such as active infections, noninfectious inflammatory processes, benign neoplasm 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 a cystic lung disease. 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, frequently demonstrate standardized uptake value (SUV >2.5) similar to malignant lesions [64]. 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 [65]. However, it is necessary to have more perspective data to guide the clinical use of FDG-PET in the diagnosis and follow-up of LCH. After PLCH diagnosis is made, it is necessary to follow the course of the disease evaluating clinical parameters, chest radiography or better 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 confirmed by the study of Soler et al. in which a cor-

relation 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, suggesting a reactivation of the disease [42]. 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].

RB-ILD

Introduction

Bronchiolitis is a generic term used to describe an inflammatory process regarding the small airways that may be the consequence of cigarette smoke, infections, aspiration, environmental agents, drugs or underlying systemic disorders such as connective tissue diseases and transplantation rejection [66]. 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 post-mortem findings showed the presence of clusters of pigmented macrophages in respiratory bronchioles and neighboring alveoli [67]. These changes are common in cigarette smokers and the term respiratory bronchiolitis (RB) is appropriately used to indicate small airways inflammation in smokers. In 1987 Myers et al., studied six patients 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 [68]. These were the first cases, described in literature, of respiratory bronchiolitis associated with an inflammatory involvement of the interstitium. The term "respiratory bronchiolitis with associated interstitial lung disease" (RB-ILD) appeared in 1989 in a study of Yousem et al. concerning the histopathological differences between this new entity and other interstitial lung diseases. This 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 [69]. Thus, the diagnostic suspect should also be based on clinical presentation. RB is usually asymptomatic while symptoms, such as dry cough and dyspnea, are more often present in RB-ILD [67].

Cottin et al. studied a population of 79 patients affected by spontaneous pneumothorax who underwent surgical biopsy and RB was found in 88.6 % of smoker patients, while RB-ILD was found in 67.1 % of patients [70]. Emphysematous lesions were present in a third of patients demonstrating the high incidence of emphysema and spontaneous pneumothorax in RB and RB-ILD. However the pathogenesis, explaining the mechanism by which tobacco induces change in small airways and the development of emphysema and bullae, remains to be clarified.

The occurrence of RB is uncommon when there is no smoking exposure as described by Fraig et al. who studied a population of 109 patients affected by RB of which 98 % were smokers (current or former smokers). Only two of the 109 patients with RB were non-smokers [71]. Woo et al. described a case of a non-smoker woman with radiological and histological features of RB–ILD, who was continuously exposed to cigarette smoke because of her job. Few studies have focused on the incidence of RB in smokers and in non-smokers so that the role of second-hand smoke or environmental exposure in the cause of respiratory bronchiolitis has not been clearly described [72].

Epidemiology

Fraig et al., in a study performed on lung biopsy of smokers, described the presence of RB in all smokers and about 50 % of former smokers [71]. 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 smoking is less obvious, although the percentage of smokers developing RB remains 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 are cough and dyspnea, inspiratory crackles may be present and more rarely digital clubbing. Lung function tests are nonspecific, they can be normal, but is not unusual to find obstructive, restrictive or mixed obstructive/restrictive patterns. Obstructive pattern is a typical sign of smoking exposure and RB, while mixed pattern can orientate the diagnosis towards an association of RB with interstitial lung disease. Diffusing capacity is usually

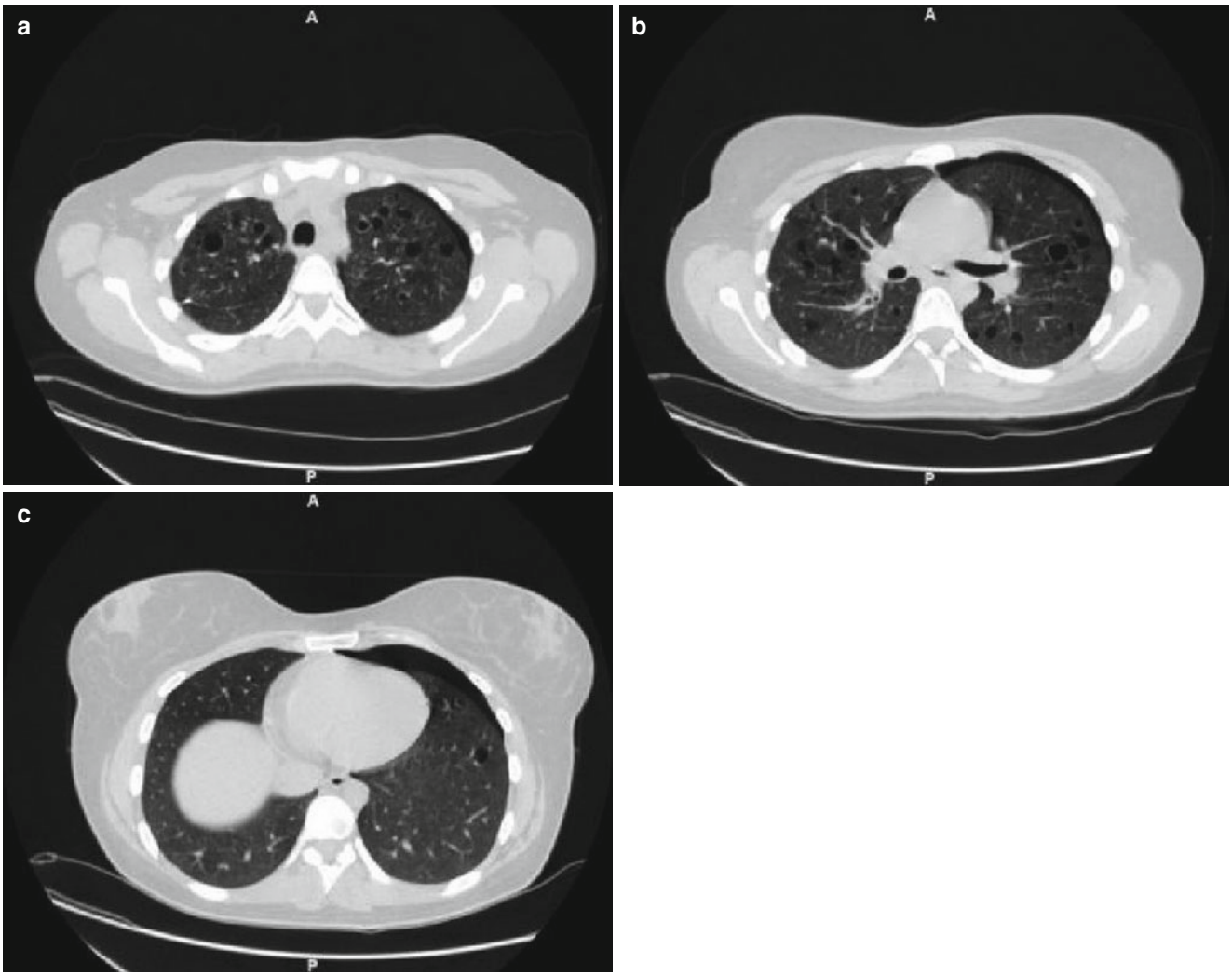

Fig. 28.7 (**a**) High-resolution CT scan demonstrates a small left pneumothorax and bilateral irregular cysts, with thin walls. (**b**) Some of these cysts appear to coalesce into larger and irregular structures with bizarre shapes. (**c**) Typical lesion distribution with relative sparing of lower lobes

decreased and it may be a useful guide to define the severity of the disease more than in making diagnosis, low DLCO values may in fact indicate other conditions related to cigarette smoking such as emphysema [26].

Histopathological Findings

According to Myers et al., who first described the disease, RB-ILD is histologically indistinguishable from RB [68]. The histological hallmark of both disorders is represented by the accumulation of alveolar macrophages within respiratory bronchioles. Macrophages are characterised by eosinophilic cytoplasm, with brown granular pigmentation representing constituents of cigarette smoke. It is also possible to observe a chronic inflammatory cell infiltrate within bronchiolar walls, while no honeycomb change or fibroblastic foci are present (Fig. 28.8). Myers and colleagues suggested that the main difference between RB and RB-ILD is based on the extent of the fibrosing and inflammatory process that in RB-ILD involves also adjacent alveolar walls [68]. Nakanishi et al. correlated the histopathological findings of RB-ILD patients with their radiological features. Accumulation of macrophages within bronchioles was associated to 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 instead the result of mild alveolar fibrosis accompanied by inflammation and, once again, by the accumulation of macrophages. In more advanced stages of the disease, HRCT showed areas of linear and reticular opacity that histologically corresponded to alveolar and sub-pleural microcystic fibrosis [73]. Craig et al. compared the histological features

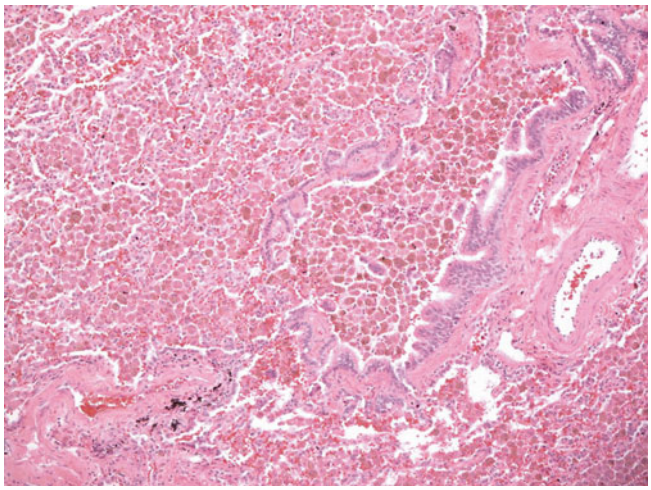

Fig. 28.8 RB consisting of distorted bronchioles with aggregates of "golden" macrophages into and around the bronchioles (Courtesy of Professor G. Rossi. University of Modena-Reggio Emilia, Italy)

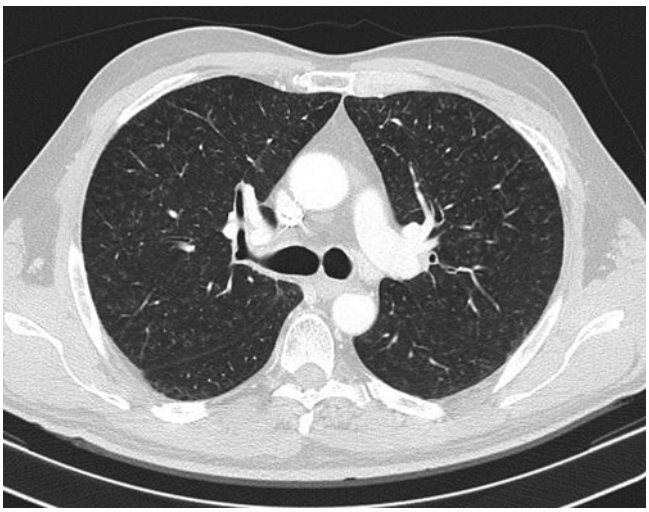

Fig. 28.9 HRCT of a patient affected by RB-ILD showing poorly defined centrilobular nodules (Courtesy of Professor N. Sverzellati. University of Parma, Italy)

of DIP and RB-ILD studying their clinical and radiological correlation [74]. They studied 24 patients with RB-ILD and 25 with DIP. The typical histological feature of the two entities is the presence of intralveolar macrophages characterized by pigmented cytoplasm and associated to variable interstitial fibrosis and chronic inflammation. RB-ILD lesions usually have a bronchocentric distribution, while DIP lesions are diffuse within pulmonary acini. They also found a significantly greater extent of interstitial fibrosis, eosinophilic infiltration and lymphoid follicles in DIP compared to RB-ILD. Yousem and coworkers, examined nine cases of patients with dyspnea, mixed obstructive/restrictive pattern on lung function, reduced DLCO and radiographic features of RB-ILD showing centrilobular nodules, ground glass opacities and emphysema. Surprisingly, lung biopsy revealed an extensive collagenous thickening of the alveolar septa with a patchy and sub-pleural distribution characteristic of nonspecific interstitial pneumonia (NSIP). This study confirms how difficult the differential diagnosis of these diseases may be, and underline the role of smoking as a potential cause of fibrotic lung diseases [75].

Radiologic Findings

Chest x-ray is normal in up to 20–30 % of cases, 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 [26]. The most common HRCT findings are thickening of the bronchial walls, centrilobular nodules prevalent in the upper lung zones and ground glass opacities (Fig. 28.9). Heyneman et al. compared the predominant HRCT features in a cohort of patients affected by RB, RB-ILD and DIP observing that in all these conditions centrilobular nodules and ground glass opacities represent the most common radiological pattern [76]. In RB-ILD these abnormalities are more extended compared to RB and characterized by the presence of areas of reticulation suggesting underlying interstitial fibrosis though in the absence of honeycombing and traction bronchiectasis. However, does not exist a radiological cut-off indicating the disease extent at which RB becomes 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, usually bilateral, moderately symmetrical, peripheral and with a lower zone distribution. Basal, interlobular opacities can be associated with small peripheral cystic spaces with traction bronchiectasis. Even NSIP is marked by the presence on CT scans of ground glass opacities, but combined in this case, with irregular linear or reticular opacities and scattered micronodules with 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 [77].

Prognosis and Therapy

A number of studies that have linked smoking with the insurgence 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 improve-

ment. Symptoms and DLCO values were both improved after smoking cessation as well as ground glass opacities and centrilobular nodules on CT scans. It was also observed a significant correlation between the change in DLCO and the reduction of centrilobular nodules and ground glass opacities [73]. Sadikot et al., described two cases of biopsy-proven RB-ILD with dyspnea, severe lung function involvement and respiratory failure. Patients were encouraged to stop smoking and this led to considerable clinical and functional improvement [78]. Mavridou et al. showed a case report of acute RB-ILD in which smoking cessation alone was not adequate, requiring steroid treatment. A 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 [79]. Similarly, Woo et al. described a case of RB-ILD occurring in a patient exposed to second hand cigarette smoke. The patient treated with high dose of corticosteroids showed HRCT improvement of ground glass opacities and centrilobular nodules extention [72]. 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 restrictive patterns and severe DLCO reduction. Seven patients were treated with steroids, associated to cyclophosphamide or azathioprine in six cases. The patient 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, Portnoy et al. in 32 patients with RB-ILD, described a clinical and functional decline in spite of smoking cessation and steroid treatment. Clinical and functional improvement was only described in a minority of patients independently by smoking cessation, suggesting that symptomatic or functional improvement are not connected to the therapeutic intervention adopted. These studies suggest that the prognosis of RB-ILD is not always as good as usually believed even though it is characterized by a prolonged survival and death secondary to its interstitial lung involvement is really rare [80]. 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 association of corticosteroid and immunosuppressant is still controversial, it is instead evident that patients with RB-ILD should be strongly incentivized to stop smoking and possibly encouraged to follow a smoking cessation program. However, the real effectiveness of smoking cessation, corticosteroids or immunosuppressant in the treatment of RB-ILD remains a clinical dilemma and needs to be further evaluated.

Desquamative Interstitial Pneumonia

The term "desquamative interstitial pneumonia" was originally coined by Liebow et al. who believed that intralveolar cells, typical of this disease, were reactive alveolar pneumocytes that had "desquamated" from the alveolar surface [81]. Later, electron microscopy, demonstrated that these cells were alveolar macrophages, even though the definition of "desquamative interstitial pneumonia" remained in the classification of ILDs and is still used today. Early studies, proposed DIP as the cellular phase of usual interstitial pneumonia (UIP) because of some similarities in histopathological features [82]. This idea was not sustained by Carrington et al., who highlighted on poor prognosis for UIP and the absence of response to corticosteroid therapy in comparison with DIP, concluding that DIP and UIP are distinct entities characterized by different pathogenesis and natural history [83]. 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 histopatological similarities with 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 a reaction of small airways and lung parenchyma to cigarette smoke [75]. In another study Craig et al. showed that only 60 % of DIP patients have a history of cigarette smoking exposition [76]. 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 lung biopsy confirmed a diagnosis of DIP [84]. 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 [85]. 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 [86]. 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 [87]. 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 [83]. 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 [76, 83] almost 90 % of DIP patients were smokers or had a cigarette smoke exposition, even if, as describe above, DIP can be the radiological and histological pattern of presentation in autoimmune disorders or in drugs 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 [26]. 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 [88].

Histopathological Findings

Histopathological diagnosis of DIP is difficult because of the similarities with 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, so that differential diagnosis may be difficult [89]. 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. 28.10). However, histological differential diagnosis between DIP and RB-ILD is based not on the typology of lesions but on their extension: DIP affects the lung in a more uniform, diffuse manner and lacks of the more limited bronchiolocentric distribution observed in RB and RBILD. Despite these differences, it has been hypothesized that RBILD and DIP are two extremes of a spectrum of reactions of small airways and alveoli to cigarette smoking [76]. Other authors, consider DIP and RBILD as distinct entities, characterized by different presenting features and clinical courses. Wells et al. sustained the idea of DIP and RB-ILD as separated entities because of differences concerning 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 therapy indication (marginal in RB-ILD and necessary in DIP) [89]. However, in the differential diagnosis of DIP other ILD should be considered because many ILD patients are current smokers and often show, on lung biopsy, intralveolar macrophage accumulation as a consequence of smoking. In these cases, clinical and anamnestic information may be helpful for the diagnosis.

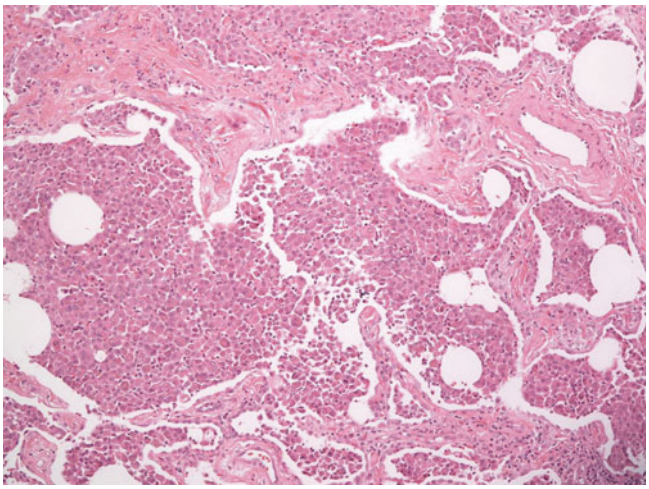

Fig. 28.10 DIP pattern is characterized by an homogeneous, jaline interstitial fibrosis with pools of golden histiocytes into the dilated alveolar spaces (Courtesy of Professor G. Rossi. University of Modena-Reggio Emilia, Italy)

Radiological Findings

The radiologic pattern is nonspecific and include ground glass areas and reticular or nodular opacities with a basal predominance as described by Liebow et al. [81]. The prevailing abnormality at HRCT is represented by ground glass attenuation that may be peripheral, patchy or diffuse and often with a basal sub-pleural predominance (Fig. 28.11) [26]. 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

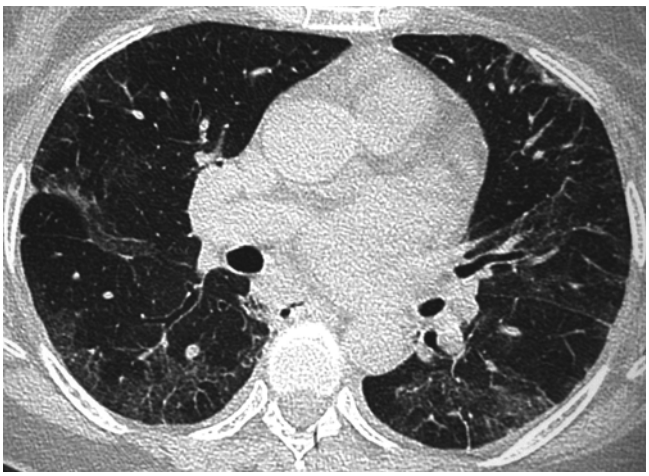

Fig. 28.11 high resolution CT image obtained through the mid lungs showing peripheral reticulation and bilateral patchy ground glass in a patient affected by DIP (Courtesy of Professor N. Sverzellati. University of Parma, Italy)

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 large prevalence of ground glass opacities in DIP [90]. Craig et al. interestingly 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 suggesting a possible evolution of DIP in NSIP [74]. 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 prevail in RBILD [91]. 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 consolidation areas [76].

Prognosis and Therapy

The objective difficulties in making the correct diagnosis 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 [83]. Baloira et al. estimated a 10 years survival rate of 70 %, while no death occurred in RB-ILD patients in the same period of follow up [88]. It has been also reported a 27.5 % mortality rate 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 [69]. Although the correlation between DIP and cigarette smoke, has not been completely demonstrated, smoking cessation is the primary treatment for DIP and may lead to disease regression as shown in different studies that reported spontaneous remission after smoking cessation with no recurrence of disease in a 4 years follow up time [92, 93]. In those cases, where smoking cessation alone does not stop disease progression, a steroid treatment is recommended. There is not sufficient evidence of corticosteroids effectiveness in the treatment of DIP, but they are used, after smoking cessation, according to signs of clinical, functional and radiological decline. Usually their dosage is of 40–60 mg daily with a gradual tapering of dose over a 6–9 month period [94]. 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 months follow up period. All DIP patients presented ground glass opacities in mid and lower lobes with sub-pleural distribution on the starting 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 it is possible to associate an immunosuppressant, even if there are not specific studies proving its efficacy in comparison to corticosteroids alone [95]. Despite smoking cessation and corticosteroid therapy, DIP can progress to end stage disease and lung transplantation 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 while it is much less recognized its role in causing a group of interstitial lung diseases defined “smoking related-interstitial lung diseases”, which includes RB-ILD, DIP, and PLCH. The correlation between cigarette smoke and these diseases is sustained by solid epidemiological data based on different case series of patients showing a preponderance of smokers in SR-ILD. It has been also 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 yet, but it has been hypothesized that cigarette smoke, in some predisposed individuals, may

cause an excessive inflammatory and/or fibrotic response both at 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, on HRCT presents 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 render the diagnosis easier. It is obvious that radiological findings should be inserted in an appropriate clinical context that must consider 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 performed. Sometimes not even the histological features allow the correct diagnosis because DIP and RB-ILD mat have very similar histopathological patterns. SR-ILDs are complex and rare diseases and their real incidence is probably underestimated because of the problematic diagnostic approach that requires a perfect integration of pulmonary, radiological and pathological knowledge. Furthermore, many issues regarding pathogenesis, clinical evolution and treatment strategies remain unresolved. New and larger studies are needed to describe and better define the clinical course of SR-ILDs and the different response to smoking cessation, as well as to corticosteroid and immunosuppressant treatment. Most importantly, future studies should be addressed to the comprehension of what makes some smokers predisposed to develop SR-ILD in comparison to smokers who will not develop the disease.

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Rare Causes and the Spectrum of Hypersensitivity Pneumonitis

29

Jean-Charles Dalphin and Anne Gondouin

Introduction

Hypersensitivity pneumonitis (HP) is the term used to describe a disease previously referred to as extrinsic allergic alveolitis or allergic alveolitis. It is an immunologic lung disease that occurs in pre-sensitized subjects: the chronic or repeated inhalation of finely dispersed antigens from a wide variety provokes a hypersensitivity reaction with granulomatous inflammation in the distal bronchioles and alveoli. The causative antigens can be classified in three broad categories: microorganisms and molds, animal and insect proteins, and chemical compounds. In many cases, causal antigens remain undeterminated. The prevalence and incidence of HP vary considerably, depending on disease definitions, methods of establishing diagnosis, intensity of exposure, environmental conditions and host/genetic risk factors that remain poorly understood [1, 2].

Although frequently described, there is currently no clear definition of HP. The HP Study Group defined it simply as "a pulmonary disease with symptoms of dyspnoea and cough resulting from the inhalation of an antigen to which the patient has been previously sensitized" [3, 4]. The NHLBI/ORD workshop report did stress the need for precise and standardized diagnostic criteria [2]. Several different diagnostic criteria have been proposed, all with significant concerns that limit their utility [5–8]. Nevertheless, all of the latter propositions recognize the exposure to a known cause as a major compulsory criterion. Moreover, in the HP Study, devoted to identifying independent clinical predictors of HP, the criterion "exposure to a known offending antigen" was 5–20 times more powerful than the others with respect to clinical symptoms, physical examination and precipitating antibodies. These results highlight the major role of exposure, that is to say the precise identification of causes, in HP.

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Diagnosis

Clinical Behavior and Classification

The clinical features of HP have been classified into acute, subacute and chronic forms [6]. In the acute form, influenza-like symptoms predominate, with chills, fever, cough, fatigue, myalgias and arthralgias that begin to 4–8 h after exposure and last from hours to days. Dyspnoea is not constant. The subacute form appears progressively over several days to weeks with dyspnoea and cough. It may evolve into severe respiratory failure leading to hospitalization. The chronic form presents an insidious onset over a period of months or years with cough, dyspnoea, fatigue and weight loss [3]. The distinction between the stages of HP is difficult as they likely represent different manifestations of a single disease that may be related more to the pattern of antigen exposure than to the offending antigen itself [3]. This statement is supported by the finding of considerable overlap in the clinical manifestations of patients with farmer's lung and those with bird-HP [9, 10]. It is worth noting that this classification was suggested before the use of computed tomography of the chest to describe HP. Moreover, it is complicated by the fact that chronic HP may correspond to an active form as well as to a residual one. Data from the HP Study [4] were recently used to divide a cohort of patients with HP into a restricted number of categories (clusters) with maximally differing clinical patterns [11]. One hundred and sixty eight patients were included in the analyses. A 2-cluster solution best fitted the data. Patients in cluster 1 (n=41) had more recurrent systemic symptoms (chills and body aches) and normal chest radiographs than those in cluster 2 (n=127), who showed significantly more clubbing, hypoxemia, restrictive patterns

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Table 29.1 Clinical, physiologic, radiologic, histologic and outcome features of hypersensitivity pneumonitis

	Type 1 HP (e.g., farmer's lung)	Type 2 HP (e.g., bird fancier-s lung)
Exposure	Usually massive and intermittent	Usually chronic insidious
	Usually microorganisms (fungi and actinomycetes)	Usually lowdose of avian antigens
Clinical behaviour	Primarily acute/subacute : higher frequency of fever and recurrent episodes. Usual phlegm	Recurrent BFL: cough and mild exertional dyspnea, low-grade fever
	More recurrent systemic symptoms (chills, body aches)	Insidious BFL: progressive dyspnea; clubbing
Lung function tests	Mild restrictive abnormalities that resolve	Restrictive pattern
	Airflow obstruction (usually mild) seen in chronic disease	Hypoxemia at rest or exercise common
Lung imaging studies	Chest X-ray: frequently normal	Chest X-ray: frequently abnormal
	HRCT: ground glass opacities, predominating in the lower lobes, fine centrolobular nodules, hyperluscent areas	HRCT: irregular reticular opacities, traction bronchiectasis and honeycombing superimposed to subacute changes (e.g. ground-glass opacities, nodules, hyperluscent areas)
	Most frequent long-term sequelae: mild emphysema often sparing the upper parts of the lung	
BAL and precipitins	Non-specific for differentiating both types	Non-specific for differentiating both types
Lung biopsy	Small, poorly-formed noncaseating granulomas located near bronchioles	Ill-formed granulomas (may be difficult to identify)
	Peripheral airways: proliferative bronchiolitis obliterans, characterized by fibroblast proliferation and an organizing intraluminal exudate that occludes bronchioles from within	Fibrotic pattern: NSIP-pattern or UIP-like pattern
		Peripheral airways: constrictive bronchiolitis
Outcome	Usually resolves	Poor, often progress to fibrosis
	Chronic exposure may lead to chronic bronchitis or emphysema	Possible acute exacerbation of chronic form without further exposure

Data from Refs. [9, 11, 13, 14–20]
Definition of abbreviations: *BAL* bronchoalveolar lavage, *BFL* bird fancier's lung, *HP* hypersensitivity pneumonitis, *HRCT* high-resolution computed tomography, *NSIP* nonspecific interstitial pneumonia, *UIP* usual interstitial pneumonia
*Coexistence of fibrosis and emphysema is possible

on pulmonary function tests and fibrosis on high-resolution chest CT (HRCT). There was considerable disagreement between the 3-stage classification and the results of this analysis [11]. Cluster 1 looks most like the classical acute form of HP and tends to occur in individuals exposed to microorganisms (especially farmer's lung patients). Conversely, cluster 2 corresponds to the classical chronic form of HP and occurs mainly in individuals with chronic exposure to bird antigens. Most of the classic subacute forms likely belong to cluster 1. The course and prognosis of HP most likely follow this new proposition for classification and may be dependent on the type and the pattern of exposure: massive and intermittent exposure to – especially, but not only – microorganisms, mainly produce a cluster-1 form and may lead to chronic bronchial obstruction with emphysema [12]. Chronic exposure to a low level of – especially, but not only – avian antigens, mainly produces a cluster-2 form and may lead to a restrictive pattern with fibrosis. These two types of HP are presented in Table 29.1.

Diagnostic Methods

There are no specific tests or biomarkers to date that allow a consistent diagnosis of HP. Therefore, it is, by necessity, based on the conjunction of clinical, radiological, functional, immunological and histopathological diagnostic indicators among which none is actually specific to the disease. Of these, histopathological signs are the most reliable but open-lung biopsy is more and more rarely performed. HRCT scans and data from bronchoalveolar lavage (BAL) are considered to be the most useful non-invasive tools. The first often show pathognomonic features; the second is highly sensitive. Finally, in absence of standardization in the inhalation protocol and in the criteria defining a positive response, specific provocation tests are not recommended.

Histopathology

Most cases of HP, whether acute or subacute, include the following histologic features in variable proportions [21]:

1. cellular bronchiolitis, which is the presence of chronic inflammatory cells lining the small airways, sometimes with resultant epithelial ulceration;
2. diffuse chronic interstitial inflammatory infiltrates, primarily consisting of lymphocytes and plasma cells but often including eosinophils, neutrophils and mast cells;
3. poorly circumscribed interstitial non-necrotizing (non-caseating) granulomas consisting of lymphocytes, plasma cells and epithelioid histiocytes, with or without giant

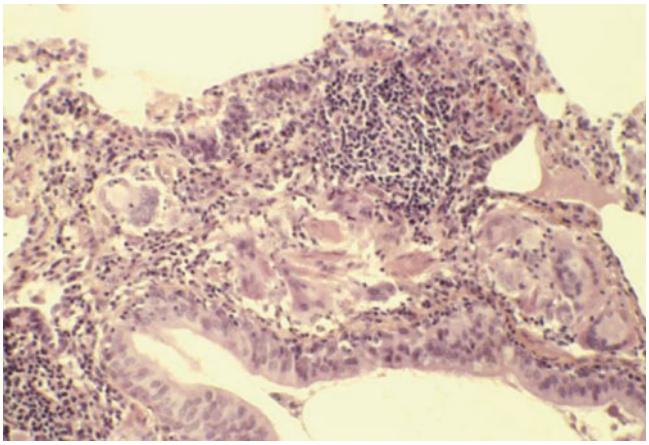

Fig. 29.1 Peribronchiolar poorly formed granuloma with giant cells and numerous lymphocytes. Absence of follicular organization. Type 1 farmer's lung disease

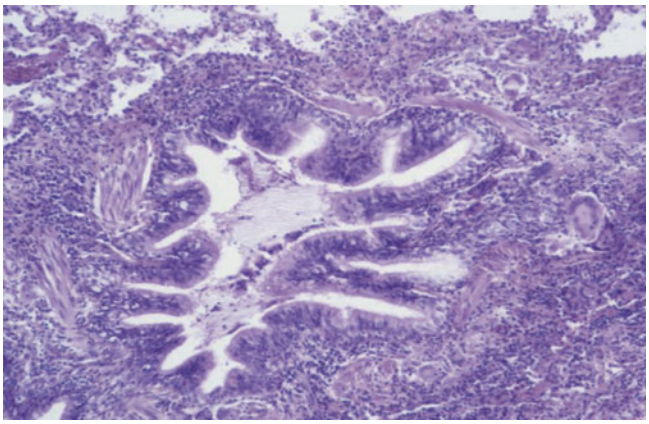

Fig. 29.2 Interstitial mononuclear and granulomatous infiltration around the bronchiole giving a constrictive bronchiolitis feature. Hypersensitivity pneumonitis due to moulds on a ceiling

cells (Fig. 29.1). Both the interstitial mononuclear and the granulomatous inflammation tend to form around bronchioles and obliterative bronchiolitis may occur (Fig. 29.2). Scattered areas of organizing pneumonia with intraluminal bronchiolar polyps also are common;

4. individual giant cells in the alveoli or interstitium. These cells may contain inclusions of endogenous metabolic products, such as cholesterol clefts, Schaumann bodies and lucent birefringent oxalate crystals.

The bronchiolitis may include variable degrees of peribronchiolar fibrosis and hyperplasia of the bronchiolar epithelium, a characteristic but non-specific finding [22].

In some patients with insidious onset disease, emphysema may be a prominent component. Non-specific interstitial pneumonitis (NSIP), usual interstitial pneumonia (UIP) and bronchiolitis obliterans organizing pneumonia might be the sole histological expressions of the disease [20]. In patients

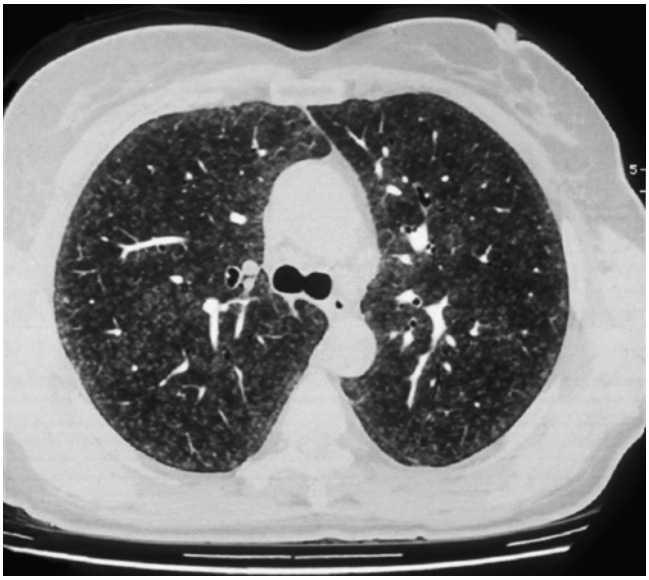

Fig. 29.3 Diffuse ill-defined centrilobular small nodules. Farmer's lung disease

in whom the pattern of fibrosis is consistent with UIP or NSIP, the presence of giant cells, granulomas, areas of interstitial granulomatous inflammation, or peri-bronchiolar fibrosis should suggest the diagnosis of HP.

Imaging Features

Chest radiography is used to determine the cause of illness and rule out the others. Up to 20 % of individuals with active HP have normal chest X-rays [23].

HRCT reflects histopathologic findings with precision by showing direct (mainly centrilobular opacities and ground-glass opacities) and indirect (mainly hyperluscent area and air-trapping) images.

Ground-glass opacities are usually bilateral and symmetric, but sometimes patchy; they generally predominate in the middle part of the lungs. These opacities usually represent chronic interstitial inflammation but occasionally may be caused by fibrosis or organizing pneumonia. Another characteristic direct feature is the numerous small round centrilobular opacities, usually less than 5 mm in diameter (Fig. 29.3). These centrilobular ground-glass opacities sometimes have relatively well-defined borders and are referred to as nodules. These abnormalities represent cellular bronchiolitis, peribronchiolar interstitial inflammation, or, less frequently, focal organizing pneumonia. The third major finding is hypoattenuation and hypovascularity of scattered secondary lobules giving sometimes a mosaic aspect (Fig. 29.4). Hypoattenuating regions that persist on expiratory HRCT are indicative of air-trapping (Fig. 29.5), which is caused by bronchiolar obstruction, often favored by the presence of mucus. The combination of patchy ground-glass

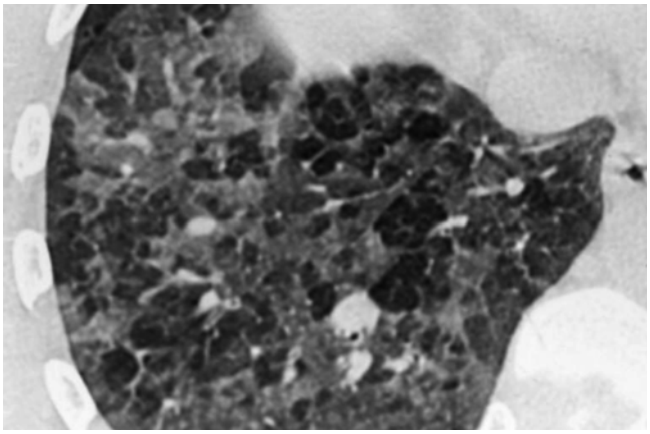

Fig. 29.4 Ground-glass opacities and hypoattenuation of scattered secondary lobules giving a mosaic pattern. Hypersensitivity pneumonitis due to molds in wood sewage

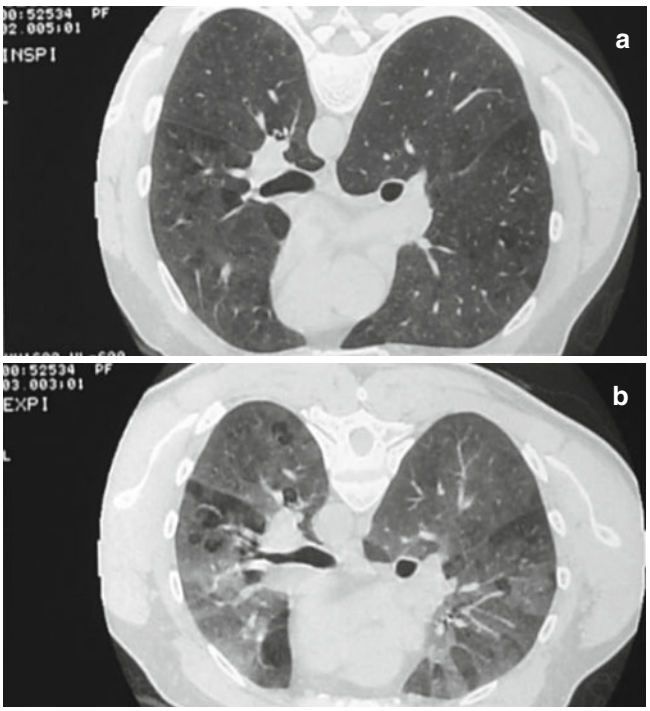

Fig. 29.5 Bilateral ground-glass opacities, associated with hyperlucent segmentar areas (**a**). Expiratory slices show an accentuation of density of ground-glass without loss of volume of hyperlucent aeras signing air trapping due to bronchial obstruction (**b**)

opacities, normal regions and air-trapping on HRCT is sometimes referred to as the headcheese sign [21]. Bronchiolar wall thickening may also occur. Lung cysts have been found occasionally and are probably caused by obstruction of bronchioles (Fig. 29.5). Focal consolidation, which often represents organizing pneumonia, is rarely present. Mediastinal lymph-node enlargement does not rule out the diagnosis of HP [17]. Pulmonary arteries are occasionally enlarged, presumably reflecting pulmonary arterial hypertension [24]. In type-1 patients, especially farmer's lung patients, centrilobular emphysema may develop [17]. When fibrosis is present, HRCT demonstrates reticulation, mainly in the middle portion of the lungs or evenly throughout the lungs but with sparing of the extreme bases [21, 25]. Honeycombing may occur, resembling that in patients with idiopathic pulmonary fibrosis (IPF) [26]. When fibrotic HP is compared with IPF or NSIP, the CT-features favoring a diagnosis of HP are lobular air-trapping, centrilobular ground-glass opacities and absence of lower-lobe predominance [21, 26].

Bronchoalveolar Lavage

BAL plays a major role in the investigation of patients suspected of having HP in that a normal number of lymphocytes rules out all but residual disease [27]. BAL is considered normal when the percentage of lymphocytes is less 30 % in nonsmokers and 20 % in smokers. Nevertheless, a significant increase in neutrophils can be observed when BAL is carried out shortly after exposure [28]. In this situation, the BAL sample can consist mainly of macrophages and neutrophils, with less than 30 % of lymphocytes. Soon afterwards, lymphocytes predominate. Lymphocytosis is also seen in BAL fluid from patients with a history of HP but with no recent activity, making it a very instructive tool for retrospective diagnosis. BAL lymphocytosis is, however, poorly specific as it may be seen in many other lung diseases [29]. A classic finding is a ratio of CD4 to CD8 lymphocyte subsets that is less than 1 (the normal ratio is 1.8). CD4/CD8 ratio is probably affected by the clinical form of HP, exposure to tobacco smoke, the type and dose of inhaled antigen and the time elapsed since antigen exposure. A recent multicenter study in France retrospectively assessed the diagnostic value of BAL in 139 HP cases, mainly farmer's lung: only 34 % of the subjects showed a CD4/CD8 ratio less than 1 [30]. Hence, the usefulness of the CD4/CD8 ratio to diagnose HP is highly questionable.

Specific Serum Antibodies

The presence of circulating antibodies against the putative offending antigen(s) is useful for diagnosis. Indeed, the results of the HP study demonstrated that positive serum antibodies are a significant predictor of HP (odds ratio: 5.3; 95 % IC: 2.7–10.4) after taking antigen exposure into account [4]. The selection of antigens to be tested often needs to be determined locally according to the prevalent antigens. In Eastern France, by using a panel of antigens shown to be responsible for farmer's lung rather than a classic standardized panel, serological tests showed high figures for both negative predictive values and specificity (from 89 to 95 % according to prevalence of the disease). In that study however, sensitivity was low with 11 out of the 31 tested HP cases negative. Additional investigations by microbiological

samplings in the environment of these negative subjects allowed to identify antigens not present in the initial panel. Eight of the 11 false-negative HP cases became positive after testing these unusual antigens. These results highlight the importance of (1) the use of antigens proven to be representative of exposure, (2) the knowledge of unusual antigenic exposure and (3) sampling the patient's environment.

Several methods of determining precipitins or total IgG antibodies have been described. Enzyme-linked immunosorbent assay (ELISA) is largely used because this technique is standardized. The consistency of 4 serological techniques (electrosyneresis, Ouchterlony double-diffusion, ELISA and Western-blot) was recently evaluated in France. Electrosyneresis on cellulose acetate was the most relevant diagnostic tool to discriminate farmer's lung from healthy exposed farmers (sensitivity 87 %, specificity 100 %) [31].

All of these considerations concern tests against organic antigens: microorganisms, moulds or animal proteins. In the case of HP due to chemical substances, isocyanates for example, serological tests have not been demonstrated to be useful or even interpretable.

Pulmonary Function Tests

Pulmonary function tests (PFTs) have no discriminative properties in differentiating HP from other diffuse infiltrative lung diseases [4]. At the time of diagnosis, PFTs can be normal, or classically show a restrictive pattern (especially in type 2 HP) or sometimes reveal an obstructive pattern. In chronic disease, the pattern can be restrictive, but at least in farmer's lung, and probably in other HP due to microorganisms, the most frequent profile is an obstructive defect resulting from chronic airway involvement or emphysema [32]. Decreased carbon monoxide diffusion capacity (DLCO) is generally considered to be consistently present in HP [33, 34]. But if we strictly define abnormal values as a DLCO <80 % predicted, some HP cases have normal results [3]. Importantly, the improvement of DLCO is very low, for up to 2 years in the large follow up study by Kokkarinen et al. [34]. This slow recovery of DLCO is in agreement with the slow recovery of both histological changes and lymphocytic infiltration in HP. Hypoxemia is common, especially with exercise. Hypoxemia (at rest or at exercise) and lung volume defect recover quickly, within a few months after an acute episode [34, 35]. These abnormalities are nevertheless non-specific since similar changes are found in most interstitial lung diseases (ILDs).

Diagnostic Criteria

HP represents a diagnostic challenge due to the absence of any one feature that distinguishes it from other ILDs. The diagnosis of HP relies on a high degree of clinical suspicion, the recognition of past history of antigen exposure and conjunction of clinical, radiologic, laboratory and sometimes pathologic findings [9]. Several diagnostic criteria recommendations have been published but none has been validated, so their diagnostic accuracy is unknown [36]. The HP Study [4] is, to our knowledge, the only one to give validated diagnostic criteria. But, it evaluated non-invasive clinical criteria only. In addition, it included a large proportion of the chronic form of HP induced by continuous avian exposure, which might make it difficult to extrapolate and apply the results to HP in general.

Table 29.2 Significant predictors of hypersensitivity pneumonitis

Variables	Odds ratio	Confidence interval (95 %)
Exposure to a known offending antigen	38.8	11.6–129.6
Positive precipitating antibodies	5.3	2.7–10.4
Recurrent episodes of symptoms	3.3	1.5–7.5
Inspiratory crackles	4.5	1.8–11.7
Symptoms 4–8 h after exposure	7.2	1.8–28.6
Weight loss	2.0	1.0–3.9

Reprinted from Lacasse et al. [4] with permission

The HP Study

The objective of this prospective multicenter cohort study was to develop a clinical prediction rule for the diagnosis of active HP. Such a rule aims at helping clinicians to reach a more accurate estimate of probability of HP and to decide whether further investigation is needed to rule it either in or out [36]. Consecutive adult patients presenting with a pulmonary syndrome for which active HP was considered whatever the possible diagnosis were included in the study. The investigators had to classify each patient as HP or non-HP. The final diagnosis was based on BAL findings, HRCT and, when necessary, other procedures including surgical lung biopsy.

Multivariate analysis identified 6 significant independent predictors of HP (Table 29.2). The clinical prediction model produces an equation that expresses the probability of HP as a function of the statistically significant variables. From this equation, a table of probability for combinations of predictors was constructed (Table 29.3). For instance, farmers presenting with recurrent episodes of respiratory symptoms, inspiratory crackles and positive testing for the corresponding precipitating antibodies, the probability of HP would be 81 % (Table 29.3). A patient with progressive dyspnoea and inspiratory crackles as the only criteria in favor of HP would have a probability of less than 1 % [36]. Further investigations such as HRCT and/or BAL would be indicated in the first case; diagnosis would be excluded in the second.

Table 29.3 Probability (%) of having hypersensitivity pneumonitis

				Crackles			
				+		–	
				Serum precipitins (%)		Serum precipitins (%)	
Exposure to a known offending antigen	Recurrent episodes of symptoms	Symptoms 4–8 h after exposure	Weight loss	+	–	+	–
+	+	+	+	98	92	93	72
+	+	+	–	97	85	87	56
+	+	–	+	90	62	66	27
+	+	–	–	81	45	49	15
+	–	+	+	95	78	81	44
+	–	+	–	90	64	68	28
+	–	–	+	73	33	37	10
+	–	–	–	57	20	22	5
–	+	+	+	62	23	26	6
–	+	+	–	45	13	15	3
–	+	–	+	18	4	5	1
–	+	–	–	10	2	2	0
–	–	+	+	33	8	10	2
–	–	+	–	20	4	5	1
–	–	–	+	6	1	1	0
–	–	–	–	3	1	1	0

Reprinted from Lacasse et al. [4] with permission
All the predictors are dichotomous variables
– indicates absent, + present

The Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires (GERM'O'P) French Propositions for Diagnosis Management

These propositions cannot be considered as actual diagnostic criteria in that they have not been validated. They represent a tool for standardized diagnostic management to be used by specialists of interstitial lung diseases (Table 29.4).

Their use requires:

- access to an extensive list of causes of HP such as that used by the GERM'O'P, summarized in Table 29.1. This list of causes should be used in questionnaire form and should include some details on the circumstances of exposure as well as on the antigens responsible for the disease;
- the presence of a reference laboratory able to do environmental samplings, to perform immunodiagnosis techniques including the production of antigens and the use of appropriate immunological methods;
- HRCT with thin slices, procubitus and expiratory manoeuvres in order to detect indirect signs of bronchiolitis which may be the only abnormality in HP.

Rare, Unusual and New Causes of Hypersensitivity Pneumonitis

The Track of Offending Antigen(s)

Tracking the culprit antigen(s) is the most important thing to do when a patient presents with a respiratory syndrome for which HP is considered among the possible diagnoses. When the antigenic source is identified, the probability that a patient is suffering from HP is multiplied by 18 as compared with a patient for whom no exposure is found [4]. The presence of serum precipitins (or IgG) directed against the antigen(s) multiplies the probability of HP by 5 again [4]. Furthermore, when HP is diagnosed, identifying the precise etiology facilitates the only efficient treatment – avoiding the antigenic source. It is therefore crucial to be able to refer to a comprehensive and easily understood list of rare or newly identified causes.

However, identification of a specific antigen should not be a *sine qua non* for diagnosis, because new knowledge about antigens is generated from identifying new sources of exposure [2]. Some authors speak of HP from "unidentified

Table 29.4 Suggested working diagnostic criteria of hypersensitivity pneumonitis

1. Exposure to offending antigens: revealed by history[a] and/or microbiological investigations of the environment and/or presence of serum precipitins against antigen(s) from a standardized panel of antigen(s), or against antigen(s) present in the own environment of the individual
2. Symptoms compatible with HP and basal crepitant rales[b]
3. BAL fluid lymphocytosis[c]
4. Findings compatible with HP on HRCT
5. Decreased DLCO and/or arterial hypoxemia (or decreased blood saturation) at rest or during exercise

Adapted from Thaon et al. [37] with permission
Criteria 3 and 4 represent the "gold standard" for the diagnosis and are obligatory
Diagnosis of HP is definite when the five criteria are present. In absence, diagnosis requires a positive natural challenge and if negative, pulmonary samples for histological confirmation
[a]Requires the use of a comprehensive list of etiologies like that from the GERM'O'P questionnaire summarized Table 29.5 or like that published in Ref [37]
[b]Basal crepitant rales cannot be considered as an obligatory criteria as it is an operator-dependant indicator and must be considered as an additional criteria
[c]Except if BAL is performed very shortly after acute phase or exposure. In this case, BAL may to be done again some days later

causes". In our opinion, it would be more appropriate to say HP from "causes not yet identified".

In addition to the unusual etiologies or etiological circumstances presented in Table 29.5, we present below a brief overview of recently discovered or poorly known causes or circumstances of HP.

Home-Related Hypersensitivity Pneumonitis Due to Fungi

Fungi are probably the most frequent antigens to cause HP worldwide. They are implicated in farmer's lung disease, mushroom worker's lung, suberosis, malt-workers' lung, sequoiosis, cheese-washers' lung, woodworkers' lung, ventilation pneumonitis, humidifier's lung, summer-type pneumonitis in Japan, among others. *Aspergillus* sp., *Penicillium* sp., *Alternaria* sp., *Fusarium* sp., *Cladosporium* sp., *Trichosporon* sp., *Cryptococcus* sp., *Absidia* sp., *Eurotium* sp. are the species most often implicated. Most of these microorganisms are ubiquitous in nature; they can develop and proliferate under adequate conditions for growth: cold (for most pathogenic molds), humidity, lack of direct light, confinement or lack of ventilation and material rich in organic matter [39]. In addition to these classic risk factors, it should be noted that in Europe, at least, the growing use of wood in housing construction and of plasterboard for walls and ceilings, especially for insulation, can account for hidden moulds. The development of low-energy housing, induced notably by increasing costs of fossil fuels, can lead to unhealthy living conditions if indoor air quality is not assured by effective ventilation. Home-related HP appear sporadically, with the exception of a specific form of epidemic known as summer-type fever, which occurs almost exclusively in the summer in Japan and is most often caused by mold of the Trichosporon genus [40].

The form these HP take is similar in nature to the type-1 form described above. They resemble farmer's lung, sometimes with recurring flu-like symptoms, overall fatigue, an HRCT image presenting a somewhat ground-glass appearance, nodules and indirect signs of bronchiolitis, and nearly normal respiratory function. However, severe and/or particular forms have been described. Jacobs et al. reported cases of interstitial lung disease (HP, NSIP, chronic eosinophilic pneumonia, cryptogenic organizing pneumonia [COP], and UIP) associated with the presence of fungi in the home or workplace [41]. The authors considered that fungal contamination of the home was causative in a large majority of cases, even in non-HP cases. Fungi or their toxins might cause interstitial lung disease by mechanisms other than the immune mechanisms that lead to HP. Jarvis et al. reported several allergic respiratory diseases, including HP, in residences of a new building contaminated with extensive visible moulds (especially *Aspergillus versicolor*) on interior surfaces. Once the building was restored, the concentration of fungi was significantly reduced and no new or recrudescent cases were recorded after building re-entry [13, 42].

Environmental investigations play a major role in diagnosis. They must precede the avoidance test, which often confirms the diagnosis, and obviously remediation procedures. Investigations may be untaken by the patient, relatives, contractors, industrial hygienists or, in France and in some European

Table 29.5 Rare causes or etiological circumstances in Hypersensitivity pneumonitis (HP)

Diseases	Sources	Antigens
(a) **Hypersensitivity pneumonitis due to microorganisms and molds**		
HP in agriculture and in related activities (other than classical farmer's lung due to thermophilic actinomycetres and micromycetes that develop in moldy hay or straw or cereals)	Air-conditioner in a tractor Handling wheat during harvest Fertilizer and contaminated vegetals Weevils in cereals Compost (horticulture, market gardening…) Grain silo Endive workers Potato and onion workers Potato riddling Moldy wood chips in orchid plants Moldy rockwool used in rose plants	Gram-negative bacteria *Ervinia herbicola* *Rhizopus* sp. *Aspergillus flavus* *Streptomyces albus* *Sitophilus granarius* *Aspergillus* sp. *Saccharomyces cerevisiae* *Fusarium* sp. *Fusarium solani* *Pencillium* sp. Thermophilic actinomycetes *Aspergillus* sp. *Cryptostroma corticale* *Aspergillus niger*
Mushroom worker's lung due to spores of exotic species in Japan and in Europe (HP can also be related to exposure to thermophilic actinomycetes or micromycetes that develop in compost)	Puffball Oyster Pholiota Shiitake Enoki Tricholoma Bunashimati Maitaki Strophariaceae	*Lycoperdon* *Pleurotus eryngii* *Pleurotus pneumonalis* *Pleurotus cornucopiae* *Pleurotus ostreatus* *Pholiota nameko* *Lentinus edodes* *Penicillium citrinum* *Lyophillium aggragatum* *Tricholoma conglobatum* *Hypsizigus marmoreus* *Grifola frondosa* *Strophariaceae*
Cheese worker's lung	Molds (and sometimes mites) on various types of cheese	*Penicillium casei* *Pencillium roqueforti* *Penicillium camemberti* *Penicillium crysogenum* *Acarus siro*
Malt worker's lung	Moldy malt, moldy barley	*Aspergillus fumigatus* *Aspergillus clavatus*
Suberosis	Moldy cork (woodman or cork workers)	*Penicillium frequentum* *Penicillium glabrum* *Chrysonilia sitophila* *Aspergillus fumigatus*
Sequoiosis	Moldy redwood dust	*Aureobasidium* sp. *Graphium* sp. *Aarthrinium phaeospermum*
Peat moss worker's lung	Packing of peat moss	*Monocillium* sp. *Penicillium citreonigrum*
Bagassosis	Molds in sugar cane	*Thermoactinomyces vulgaris* *Laceyella sacchari* *Likely others actinomycetes*
Tobacco worker's lung	Molds in tobacco leaves (tobacco industry)	*Aspergillus fumigatus*
Thatched roof disease (new guinea)	Molds in the roof	*Saccharomonospora viridis*
Paprika worker's (or splitter's) lung	Paprika dust	*Mucor stonolifer*
Dry sausage worker's lung Salami brusher's disease Chacineros lung	Sausage powdering or labelling. Salami brushing. Molds on cold cuts	*Pencillium camenberti* *Penicillium nalgiovense* *Penicillium candidum*
Greenhouse worker's lung	Contaminated rockwool	*Aspergillus niger*
Wood HP Woodman's lung Wood trimmer's disease Maple bark disease Wood pulp worker's disease	Molding on wood material: trees, bark, maple, sawdust, pellets, chips…	*Cryptostroma corticale* *Penicillium* sp. *Paecilomyces* sp. *Rhizopus* sp. *Trichoderma Koninjii*

Table 29.5 (continued)

Diseases	Sources	Antigens
Wine grower's HP	Grey rot on grapes Red spider	*Botrytis ciberea* *Panonychus ulmi*
Humidifier lung Air conditioner lung Ventilation pneumonitis	Contaminated forced-air/cooling systems Contaminated humidifiers Misting fountains Oil containers	**Thermophilic actinomycetes** *Saccharopolyspora rectivirgula* *Thermoactinomyces vulgaris* *Thermoactinomyces candidus* **Micromycetes** *Penicillium* sp. *Aspergillus fumigatus* *Mucor* sp. *Candida albicans* *Acremonium* sp. *Saccharomyces* sp. *Alternaria* sp. *Fusarium* *Aureobasidium pullulans* *Debaryomyces hansenii* *Paecilomyces nivea* *Paecilomyces variotii* **Bacteria** *Pseudomonas* sp. *Cytophaga* sp. *Staphylococcus* sp. *Bacillus* sp. *Stenotrophomonas* sp. *Acinetobacter* sp. *Flavobacterium multivorum* *Yersinia pseudotuberculosis* *Aerobacterium liquefasciens* *Klebsiela oxytoca*
Home HP related to microorganisms Familial HP Summer-type pneumonitis (or fever)	Contaminated old houses Contaminated wood dust in walls	*Trichosporon cutaneum* *Trichosporon ovoides* *Trichosporon asahi* *Cryptococcus albidus* *Epicoccum nigrum*
Home shower HP	Moldy shower curtains	*Aureobasidium pullulans*
Thatched roof lung	Dead grass and leaves	*Saccharomonospora viridis*
Residential provoked pneumonitis	Unventilated uninhabitated houses	*Phoma violacea*
Dry rot HP		*Rhodotorula rubra*
Home Merulius HP	Molds (Merulius) developing in organic (especially wood) materials	*Serpula lacrymans*
Sewage flooding HP	Homes contaminated by sewage flooding	*Cephalosporium* *Pezizia domiciliana*
Hot tub lung Sauna taker's lung Home bathtub HP	Hot tub mists Contaminated sauna water Contaminated bathtub water	*Mycobacterium avium complex* *Cephalosporium* sp.
Home HP due to varied molds	Varied circumstances in which molds develop in relation to excess of humidity, lack of ventilation, cold (for most pathogenic species), lack of direct light, and material rich in organic matter	*Aspergillus versicolor* *Geotrichum candidum* *Leucogirophana pinastri* *Penicillium expansum* *Epicoccum nigrum* *Humicolata fluscoatra* *Stachybotrys chartarum* *Botrytis* sp. *Fusarium napiforme* *And many other species previously cited…*
Steam iron lung	Water reservoir	*Aspergillus fumigatus* *Sphingobacterium spiritivorum*
Saxophone player's lung	Molds in the reed	*Ulocladium botrytis* *Cladosporium* sp.

(continued)

Table 29.5 (continued)

Diseases	Sources	Antigens
Machine operator's lung	Aerosolised metalworking fluid	*Mycobacterium immunogenum* *Mycobacterium cheloae* *Pseudomonas fluorescens*
Fruit and legume worker's lung	Molds in a cold storage house for fruit	Micromycetes
HP to *Aspergillus oryzae*	Biological detergent for cutaneous sores	*Aspergillus oryzae* antigens
HP to *Ustilago esculenta*	Sprinkling of smut spores on lacquered wares to produce a rusty colour in Japanese handicrafts	*Ustilago esculenta*
(b) **Hypersensitivity pneumonitis due to animal proteins**		
Bird breeder's or fancier's lung of unusual causes (other than classical HP due to pigeons, doves, budgerigasr, parrots, canaries, love birds, ducks, geese, turkeys, etc.)	Pheasants Wild birds Birds of prey Owls (ringing for example) Artificial flies for fishing (made with feathers or down) Pillows, quilts, comforters…containing feathers or duvet Bats (in grottos or caves)	Avian droppings, bat droppings, feathers, serum proteins…
Furrier's lung	Animal fur? Cat hair?	Proteins in animal fur? Cat hair
Pituitary snuff taker's lung	Pituitary snuff	Bovine and porcine proteins
Animal handler's lung	Rats, gerbils…	Urine, serum, proteins…
Sericulturist's lung	Silk production	Silkworm antigens
(c) **Hypersensitivity pneumonitis due to chemical products**		
Chemical worker's lung	Polyurethane foam production Paint, lake, varnish production Paint quality control Car body repair shop Molding in foundries Plastic industry Small-scale production of airbags Aginate industry (extraction from seaweed) Manufacturing of penicillin (pharmaceutical companies) Manufacturing of pyrethroid insecticides	Isocyanates TDI MDI HDI IPDI BIC TGIC Epoxidic resins Alginic acid Penicillin Pyrethrum
Dental technician HP	Dental technician trainees	Methyl methacrylate
Yacht-maker's lung	Manufacturing of fibreglass yachts	Dimethylphtalate
(d) **Hypersensitivity pneumonitis due to undeterminated substances**		
Coffee worker's lung	Coffee beans, green beans, coffee dust	Vegetals?
Tea worker's lung	Tea dust	Molds?
Inhalation of green tea leaves (for a sinusitis)	Tea?	Tea antigens, Molds
Konnyaju manufacturer lung	Konnyaku paste (food paste used in Asia); "Jelly-like food"	Konjak flour? *Hijikia fusiforme?*
Plasterer's lung (sometimes called Stipatosis or Espartosis). Described in Spain	Esparto grass is used in manufacturing plaster, ropes, hemp sandals, rush mats, parkets…	*Stipa tenacissima?* *Sacharopolyspora rectivirgula?* *Thermoactinomyces vulgaris?*
Detergent worker's disease	Detergent, cleaning powder	*Bacillus subtilis*?
Soybean HP	Animal food	Soybean antigen?
Tiger nut worker's lung	Tiger nut dust	Plant antigen? Micromycetes?
Leaf HP	Moldy hazelnut leaves	Not determinated
Entomologist's lung	Museum	Micromycetes?

Table 29.5 (continued)

Diseases	Sources	Antigens
Mollusc shell HP	Pearl nucleus worker Nacre factory worker Nacre-button worker Sea-snail shells workers	Proteic antigens from mollusc (oyster, sea-snail…) shells?
Fish meal worker's lung	Fish meal	Fish proteins?
Carmine HP	Food or cosmetic coloring	Carmine antigens?
Cow milk HP	Cow milk ingestion	Cow milk antigens?
Pet-fish food lung	Pet-fish food	Animal antigens?
Spinach powder HP	Spinach powder used in food dyes	Spinach antigens?
Mosquito-coil HP	Mosquito-coil smoke exposure	Pyrethrum?

The metal-related parenchymal lyng diseases do not include HP *stricto sensu*, but some reports describe cases related to exposure to zinc and others metals, which resemble HP. It seems reasonable to call them "HP-like"

countries, by medical advisors for indoor environment. Most of the time, contamination is strong enough to cause HP is obvious. "Smell tests" [38] constitute the first step in detecting mouldy odors on entering a potentially contaminated site. Visual inspection is the most important step in determining the specific location of contamination. Attention should be focused on visual evidence of water damage on walls and ceilings; both suggest roof leaks or plumbing problems. Forced air-heating and air-cooling systems, evaporative coolers and window unit systems are easily investigated for evidence of malfunctions that cause contamination [38]. Microorganism cultures are necessary to identify and determine a reference level of viable microbes, as well as to elaborate antigenic extracts for further immunodiagnosis procedures [43]. For identification purposes only, cultures can be obtained by direct swabbing of visible moulds. A gravity culture technique of the indoor air using electrostatic dust collectors allows to identify and establish a reference level for a specific environment and helps to ascertain the effectiveness of remediation [44, 45]. This technique is easy to perform, unexpansive and repeatedly consistent. However, samplings must last 2–4 weeks. Finally, there are several ways to measure microorganisms that use air sampling devices. Air sampling is useful when no visible source can be identified. This is increasingly the case in France due largely to excessive use of indoor and outdoor insulation.

Hypersensitivity Pneumonitis Due to Non-tuberculous Mycobacteria

The propensity of varied non-tuberculous mycobacteria (NTM) to cause lung disease varies widely and is conditioned by host factors. Non-tuberculous mycobacteria pulmonary disease (NTMPD) usually occurs in one of three prototypical forms: HP, cavitary tuberculosis-like disease or nodular bronchectasies [46]. HP has now been well described with respect to exposure to various species of NTM, especially to *Mycobacterium immunogenum* in relation to aerosols of metalworking fluids (machine operator's lung) and to *Mycobacterium avium intracellulare* in relation to aerosols of water in baths, pools, saunas and hot tubs).

Machine operator's lung is not a rare cause of HP. More than 100 cases have been published, generally in case series. Nevertheless, it is not well known by pulmonologists. This is probably due to the epidemic character of the disease with cases concentrated in a few geographical zones and absent elsewhere in the country. Metalworking fluids are widely used where metal is cut, drilled, milled or otherwise shaped with cutting tools to remove heat from both the machine tools and the product being made and to lubricate the parts, remove metal debris and inhibit metal corrosion [47]. Fluids may be pure, petroleum oils, emulsions of petroleum in a water base (semisynthetic fluids), or emulsions of synthetic oils in water (synthetic fluids). Because they contain biologically available carbon and water, water-based metalworking fluid routinely sustains microbial growth [47]. Although widely used in various types of industry, metalworking fluids from the automotive industry are the most often contaminated by NTM and therefore responsible for HP. The absence of chromium, nickel or iron and mineral oil-based emulsions are other risk factors for HP [48]. The presentation is similar to other type-1 forms of HP caused by microorganisms. The detection of specific antibodies against *M immunogenum* is very effective in differentiating case and control subjects, and even exposed and non-exposed subjects [49].

Most cases of "Hot-tub lung" are related to hot tub/spa exposure. Occasional cases have been reported for sauna exposure, aerosols in swimming-pools and aerosols in a shower or bathroom [50–52]. Several aspects of this disease are not typically related to HP and may favour an infectious hypothesis. Firstly, *M. avium intracellulare* is nearly always found in the pulmonary samples. Secondly, well-formed and occasionally necrotic granulomas with palisaded and multinucleated histiocytes, which are sometimes found, suggest a response different from that seen in other examples of HP. The co-occurrence of peripheral tree-in-bud appearance on HRCT of the chest is also consistent with NTM infection centred around small airways. Also, the elevated CD4/CD8 ratio seen in the BAL fluid is not typical of HP, although there are recent reports on increased ratios in farmer's lung [30]. Furthermore, a preponderance of obstructive physiology is seen in this disease rather than the restrictive pattern classically described in HP. This is likely due to exuberant peribronchiolar granulomatous response. However, these features are also not unusual in other HP due to microorganisms. In fact, this presentation is rather similar to that of many cases of farmer's lung. As a result of confusion regarding the pathogenesis of hot-tub lung, there is no standard approach to the treatment of this disease. Because of the extreme resistance of *Mycobacterium avium intracellulare* to most disinfectants, the continued used of tubs after decontamination and cleaning is not appropriate [53]. Anti-mycobacterial therapy is often used in association with oral corticosteroids. But many case reports describe recovery without drugs when exposure to tubs is discontinued. This was the case for the 4 patients we diagnosed in France in the past 3 years.

Several preventive measures, which need to be validated in future studies, may be helpful [52]: good ventilation of the hot-tub room, frequent cleaning of the hot-tub, frequent change of both water and water filter, superheating the tub water to 70 °C for 1 h before use, showering before getting into the hot-tub and use of disinfectants such as bromine and ultraviolet light.

Very Rare or Novel Causes of HP

Although HP has been known for many, many years, novel causes of HP continue to surface in the literature. According to Fishwick, new and novel causes of HP fall into two categories [54]: first, an anticipatable group of causes, largely microbiological in nature, and second, a rather more unusual or less intuitive group of possible causes (Table 29.5).

HP Attributable to Anticipatable Causes

HP is very often caused by exposure to fungal or bacterial microorganisms whose presence is easily suspected, as is the case for certain professions: endive workers [55], greenhouse rose growers [56], citrus [57], and onion or potato workers [58], to name a few. The same holds true for cases observed in homes where mold is present, in professional environments which cause significant exposure to organic dust; this is the

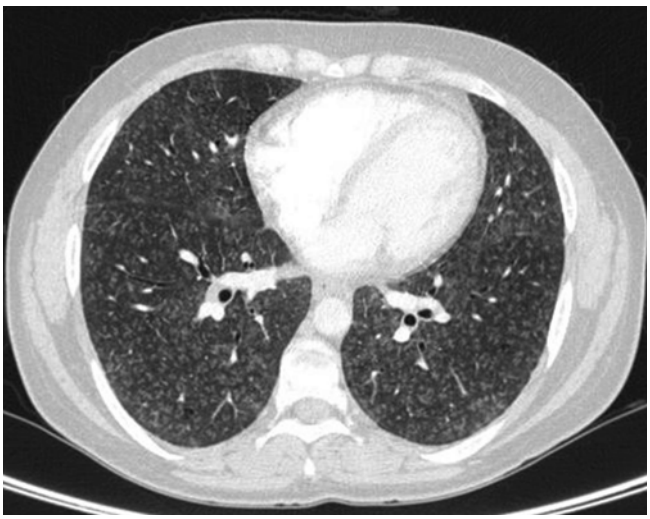

Fig. 29.6 Diffuse ill-defined centrilobular small nodules

Clinical Vignette

A 42-year-old female was admitted to the respiratory intensive care unit for severe respiratory distress. Symptoms had started 6 months earlier, with very progressive shortness of breath on exertion, dry cough, then bouts of fever reaching 39 °C, chills, headaches and arthralgia without swelling. On admission, her temperature was 39 °C, auscultation revealed wheezing, crackles and rhonchi. Arterial blood gases on room air were: arterial oxygen tension 49 mmHg, arterial carbon dioxide tension 36 mmHg, pH 7,45, HCO_{3-} 23 mmol/L. A computed tomography scan showed bilateral patchy ground-glass opacities with air trapping in the upper fields and nodular ground-glass opacities predominant in the lower lobes (Fig. 29.6) . Bronchoalveolar lavage showed a total cell count of 640 cells/mm^3, with 43 % lymphocytes, 42 % macrophages, 13 % neutrophils and 2 % eosinophils. As a comprehensive search for infectious disease in the BAL and blood was negative, HP was suspected. Her dyspnoea gradually improved within a few days without corticosteroids. On day 6 after admission, FEV_1, FEV_1/vital capacity and total lung capacity were 71, 77 and 95 % of the predicted values, respectively. The transfer coefficient of the lung for carbon monoxide (KCO) was dramatically diminished at 38 % of the predicted value. We later discovered that the onset of symptoms had occurred 2 years before admission, 3 months after she started a job in an airbag jacket factory for horseback riders or motorcyclists. She had to prepare and weld the

polyurethane airbags to a security trigger device before installing the complete airbag into the jacket. Isocyanates, composing polyurethane and vaporised during airbag welding, were rapidly considered as putatively responsible for this HP. Precipitins against a large panel of organic antigens including fungi, thermophilic, non tuberculous mycobacteria… were negative. Anti-isocyanate specific immunoglobulin E was negative as well. After being discharged from hospital, she was advised not to go back to work. Six months later, she no longer complained of dyspnoea and her physical examination was normal. Peripheral oxygen saturation was measured at 98 % on room air without dyspnoea. Chest radiographs and pulmonary function tests were normal, except for the KCO, which was only 60 % of the predicted value

case for people who work with wood, malt, cork, compost and paprika [54], for example. It is more difficult to demonstrate antigenic exposure when these same microorganisms are present in unsuspected places. Saxophone player's lung, from mould that develops in the reed [59], HP from fungal microorganisms that contaminate water reservoirs in steam irons [60] or from *Ustilago esculenta*, used in mildew powder to age lacquered knick-knacks [61]. Similarly, not everyone knows that dry sausages, salami and cold cuts in general, provide a mold-rich medium, not only the Penicillium-based dust sprinkled on sausages [62, 63]. Similar examples have been found with exposure to avian antigens. In many parts of the world, notably in Europe, quilts, pillows and comforters are still filled with goose or duck down, which can cause feather lung, a rare but not exceptional HP [64].

Conversely, it is much more difficult to incriminate artificial flies used for trout-fishing as it is not well known that they are usually made with domestic or wild bird feathers [65].

HP Attributable to Non Anticipatable Causes

This category mainly includes HP linked to chemical agents, metal-based substances, substances of animal origin or of unknown origin. Those linked to isocyanates, classic but rare, have been reported in the plastics and the paint industries [66, 67]. Other more atypical examples of exposition have been reported, as was the case of a patient found to have been making DIY airbags in her cellar for horseback riders and motorcyclists [68]. But other chemical substances have been incriminated – enzymes such as phytase, for example, used in bovine cattle feed [69]. Other studies report on exposure to alginic acid used in the treatment of seaweed [70] and pyrethrum in insecticides for professional use [71]. Numerous respiratory complications due to inhalation of metal fumes have been reported. They are not always easy to characterize, but for some of them, the clinical, radiological and immunologic presentation evoke HP [72, 73]. Stipatosis is a distinct HP described essentially in Spain; it is linked to Esparto grass, a gramineous plant used to make string, rope, baskets and plaster. This substance can lead to asthma and HP [74], but it is not known if the disease is caused by the grass or by fungal contamination.

Lastly, in many cases, most often isolated ones, the specific antigen cannot be identified, as is the case for these examples: Colimycine spray [75], bat waste [76], burns from mosquito coils [77], dust from pearls or mollusks [78, 79], animals substances [80]. Other examples are shown in Table 29.5.

Particular Features of Hypersensitivity Pneumonitis

Acute Exacerbation of Fibrotic Chronic HP

Acute exacerbation (AE) is the development of an acute lung injury that usually results in acute respiratory distress syndrome, in patients with pre-existing fibrotic interstitial pneumonia [81]. By definition, AE is not caused by infection, heart failure or reaction to aspiration of a drug. Most patients with AE have underlying UIP, either idiopathic or in association with a connective tissue disease. However, the same process has been reported in patients with fibrotic nonspecific interstitial pneumonia and fibrotic HP [82].

On biopsy, AE appears as diffuse alveolar damage or organizing pneumonia, superimposed upon the fibrosing interstitial pneumonia AE. The aetiology of AE is unknown and the prognosis is poor, even if some patients survive with high-dose steroids and/or immuno-suppresive therapy. AE is a very rare condition in chronic fibrotic HP that occurs only in rare forms with a UIP-like pattern on biopsy [83–85]. It is to be differentiated from the exacerbation of HP related to recurrence of the disease due to antigenic exposure.

Pulmonary Hypertension in Fibrotic Chronic HP

Pulmonary hypertension (PH) is a well-recognized complication of various fibrotic lung diseases such as IPF, sarcoïdosis or systemic sclerosis. The correlation between physiologic measures of fibrosis and PH is weak, suggesting that factors other than fibrosis play a role in the etiology of PH [86, 87]. Koschel et al. recently conducted a retrospective review of 73 cases of chronic HP with a doppler-echocardiography data. PH (sPAP $\geq$ 50 mmHg) was detected in about 20 % of patients [86]. There was a weak correlation between pulmonary function parameters and the underlying sPAP, in keeping with observations in IPF [87]. Apart from this retrospective study, data on PH in HP are scarce. Lupi-Herrera et al. [88] reported on 10 patients living at a high altitude who presented with HP and borderline PH (PAPm = 22.0 ± 2.0 mmHg). Costabel et al. presented data on 9 patients with HP and measurement

of hemodynamic parameters [89]. They demonstrated slight and transitory HP in some cases only. In 1997, Muracami et al. published a HP case caused by *Shiitake* mushroom spores with a marked decreased pulmonary perfusion [24]. They suspected the presence of transient vasculitis. In 2000, we published [90] the case of a 47-year-old woman admitted to the emergency unit with acute dyspnoea, severe hypoxia, marked HP and signs of right heart failure. Pulmonary embolism was ruled out. Detailed questioning and thorough examination lead to a diagnosis of a bird-related HP: the patient had been living for years in a small flat with nearly 100 exotic birds. All abnormalities disappeared a few months after antigen avoidance. There are therefore arguments for a vascular involvement in some cases of acute or chronic forms of HP, according to with Barrowcliff in his description of an early acute fatal case of HP in 1968 [91].

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Chronic Beryllium Disease and Other Interstitial Lung Diseases of Occupational Origin

30

Joachim Müller-Quernheim, Gernot Zissel, Gian Kayser, and Antje Prasse

Clinical 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. Subsequently, exposure to beryllium-containing dust in dental laboratories became known and this exposure had started at age of 18 before sarcoidosis had been diagnosed and had continued until 31 years of age. Findings typical of sarcoidosis such as unproductive cough, dyspnea on exertion, bihilar lymphadenopathy, and reticulonodular markings in the chest radiogram were still present at the age of 40 years. In-vitro lymphocyte proliferation of peripheral mononuclear cells cultured in the presence of beryllium sulphate yielded an elevated stimulation index demonstrating beryllium sensitization although exposure had been terminated 9 years earlier. 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.

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Introduction

Interstitial lung diseases (ILD) are in most cases syndromes lacking an unequivocal definition. Thus, a thorough diagnostic workup may result in clinical findings supporting the diagnosis of an idiopathic syndrome according to current definitions or even guidelines but as in the case described in the case vignette [1] an unrecognized occupational exposure may cause a disorder with an identical clinical phenotype but of toxicologic or immunologic origin. In the case of sarcoidosis a detailed occupational history identifying metal dust exposure and subsequent investigation of beryllium sensitization may result in the need to correct the diagnosis from idiopathic sarcoidosis to occupational chronic beryllium disease (CBD). 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 [2] although all diagnostic criteria for sarcoidosis have been satisfied according to actual standards [3]. Interestingly, 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 [4]. 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 [5].

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

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either of immunologic origin or can be subsumed under pneumoconiosis. However, hypersensitivity pneumonitis, silicosis, and coal workers lung are discussed elsewhere in this monograph.

Nonoccupational cases of CBD have already been diagnosed a short time after the description of CBD [6, 7] and most cases masquerade as sarcoidosis [2, 8]. Those cases may be caused by indirect or paraoccupational beryllium exposure at the workplace such as secretaries or security guards [8], by exhaust air of beryllium utilizing industries endangering residents in their vicinity [9], or by contaminated clothing brought to the home affecting family members [10, 11]. The latter is of practical relevance since a genetic background defining susceptibility for [12, 13] and progression of CBD [14] is known and this background is shared by family members which requires an extended occupational history in the diagnostic workup. Non- or paraoccupational cases have been observed in most of the disorders discussed in this chapter which widens the scope of health problems related to work. A clear dose-response relationship is commonly observed in pneumoconiosis type disorders while it is missing in many disorders with immunologic pathomechanisms.

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, flock workers disease, asbestosis, and nanoparticle induced interstitial lung disease.

Chronic Beryllium Disease

Definition

Chronic beryllium disease (CBD) is an occupational hypersensitivity disorder elicited by exposure to beryllium containing dusts and fumes at the workplace but in rare cases it may be elicited by ambient or paraoccupational exposure. It is characterized by non-necrotizing granulomata within affected organs, most frequently lung and skin. Since CBD is a perfect phenocopy of sarcoidosis the differential diagnosis relies both on occupational history giving evidence for beryllium-exposure and tests demonstrating beryllium-sensitization since 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). The diagnosis is based on the association of beryllium-exposure and -sensitization with symptomatic disease including abnormal lung function and chest-radiographs otherwise diagnosed as sarcoidosis.

Acute berylliosis is elicited by high dose exposure and shares clinical characteristics of acute sarcoidosis and toxic alveolitis. Its onset is usually immediate but may be delayed for up to 3 days. Most industrialized nations have occupational safety measures in action which prevent acute beryllium disease. Nevertheless, it may be observed when accidentally a high exposure takes place [15, 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 progress into chronic granulomatous lung disease [17].

Analogous to acute hypersensitivity pneumonitis acute berylliosis may represent rather the acute form of an hypersensitivity response than a toxic alveolitis [18]. The pathophysiological factor triggering the switch from acute to chronic disease course remains elusive.

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 [19].

Epidemiology

Soon after industrial utilization of beryllium started in the 1930s acute beryllium disease was recognized. The Atomic Energy Commission of the United States of America recognized beryllium disease in the 1940s and established a beryllium case registry that recorded cases of acute and chronic disease. The acute cases were observed among workers exposed to high levels of soluble forms of beryllium; however, the distribution of the chronic disease did not follow a linear exposure-response model and community acquired cases were observed in the vicinity of beryllium utilizing nuclear institutions. This 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 $\mu g/m^3$ averaged over an 8-h period was established. Subsequently, the diagnosis of acute disease ceased but chronic cases continued to occur although exposures were kept below this limit. In 2009, the National Institute for Occupational Safety and Health of the United States brought a Threshold Limit Value (TLV) of 0.05 $\mu g/m^3$ for an average 8-h period 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 [9] and preventive programs are able to reduce but not to eliminate sensitization [20].

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 [21]. However, the number of individuals ever exposed is assumingly much greater as the exposure by downstream use of beryllium-containing components and products is not known and could not be included in this estimate. Downstream exposure is of relevance in those nations without beryllium production but with industries utilizing beryllium containing alloys in high-tech industries but also in technical trades. Thus, in most industrialized nations importing beryllium CBD cases have been observed although testing for beryllium sensitization is limited to a small number of specialized laboratories. This observation demonstrates that measures to control beryllium-dust are urgently needed to improve workplace safety.

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. Furthermore, it could be demonstrated that beryllium-specific T-cell lines and clones exhibited a dose-dependent MHC (major histocompatibility complex) class II-restricted proliferation in response to beryllium, but did not respond to recall antigens or to other metals and beryllium-specific T cell clones disclosed a wide spectrum of rearrangements of their T-cell antigen receptor [22] and its binding to the antigen beryllium uses an unconventional binding topology [23]. A recent epidemiologic study showed that T-cell sensitization depends on the peak concentration of exposure and progression to CBD on the cumulative exposure [24]. This demonstrates that CBD is a hypersensitivity disease in which beryllium is the specific antigen. These oligoclonal beryllium reactive $CD4^{+}$T cells play a pivotal role in the immunopathogenesis of CBD. Their activation is compartmentalized to the lung and their cytokine production regulates cell migration, macrophage accumulation, and granuloma formation, and causes eventually defects of the microarchitecture of the lower respiratory tract.

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. The pulmonary histological appearance is indistinguishable from that of sarcoidosis. Demonstration of beryllium within the granulomas may add to the confidence that beryllium is responsible. Since surgical biopsies are required for in-situ beryllium detection and the technical equipment such as laser microprobe mass spectrometry, secondary ion mass spectroscopy, or electron beam analysis with energy dispersive x-ray analysis is restricted to specialized centers this way of demonstrating exposure is not used in routine diagnostic workup. In light of the hypersensitivity immune mechanism underlying CBD both the absence of beryllium in tissue analysis and the fact that biorelevant tissue concentrations are below detection limits do not exclude the diagnosis [25].

Genetics

The susceptibility to acquire beryllium sensitization progressing to CBD is linked to the individual genetic background and the presence of HLA-DPB1 alleles positive for glutamate at position 69 is the most powerful genetic risk factor known [12] which 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 [26, 27]. 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 [14] 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 [14]. 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 [28]. 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 bony involvement may imitate a systemic chronic

inflammatory disease. 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 [29]. 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 [29, 30]. In advanced cases clubbing and pulmonary hypertension with fatal courses may be seen [31]. 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 30.1.

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 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 [32]. 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 30.1. In aggregate, there are no radiographic findings differentiating CBD from sarcoidosis.

Table 30.1 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 mediatinal 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

Beryllium sensitization is the first immunologic event leading to CBD but it does not result in any physical impairment. A clear exposure dose dependency could be established [24]. 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 [33]. Further exposure and its cumulative dose define progression to CBD [24] which can take place after a short time or after a latency of years or decades. Precipitating cofactors are not known [19, 33]. Overall, under continued exposure a progression rate of 6–8 % per year of sensitized is reported [19]. After manifestation of CBD many patients suffer from slow progression of symptoms and defects of pulmonary function which can precede radiographic abnormalities [34]. However, next to those protracted courses rapid ones are observed [31]. 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 [33, 35, 36]. 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 of berylliosis is an epicritical one made when a case of non-necrotizing granulomatous disease – otherwise diagnosed as sarcoidosis – is accompanied by documented occupational (or in rare cases ambient) beryllium-exposure in combination with beryllium-hypersensitivity. Granulomatous disease of other origin such as bacterial, fungal, viral, helminthic, or metallic need to be excluded in a diagnostic workup and idiopathic disorders such as idiopathic pulmonary fibrosis may mimic CBD. The primary condition to be ruled out is sarcoidosis and the features listed in Table 30.1 are of some help. Certain clinical findings are more characteristic for sarcoidosis, such as extensive hilar adenopathy in the absence of parenchymal infiltrates (radiographic Type I of sarcoidosis) and spontaneous resolution, or have never or only rarely been reported in berylliosis, such as cystic bone lesions and cranial or peripheral nerve involvement. None of these clinical features, however, is adequately sensitive or

specific to reliably distinguish between sarcoidosis and berylliosis in individual patients. Other disorders to be considered in differential diagnosis are listed in Table 30.2.

Table 30.2 Granulomatous disorders to be considered in the diagnostic workup in suspected chronic beryllium disease

Cause of granuloma formation	Disease
Bacterial	Brucellosis, *Bartonella henselae* (cat scratch fever), *chlamydia* (Lymphgranuloma venereum), leprosy, salmonellosis, tuberculosis
Fungal	Blastomycosis, coccidiomycosis, histoplasmosis
Viral	Measles virus
Helminthic	Filariasis, schistosomiasis, trichinosis
Metallic	Aluminium-, beryllium-, titanium-, zirconium-induced lung disease
Bioaerosols	Hypersensitivity pneumonitis (*Rectivirgula faeni, Trichosporon cutaneum*)
Drugs	Allopurinol alveolitis
Unknown	Crohn's disease, granulomatous polyangitis, sarcoidosis

Box 30.1

Proposed Criteria for Working Diagnosis

Chronic beryllium disease

- 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.

Indium Tin Oxide-Lung Disease

The diagnosis requires a compatible clinical appearance combined with an occupational exposure. Clinical clues for ITO-lung disease can be:

- Reticular nodular shadows with fibrosis and cholesterol clefts +/– emphysematous lesions
- Pulmonary alveolar proteinosis without or only moderate concentration of GM-CSF autoantibodies.

Hard metal induced lung disease

- evidence of diffuse parenchymal lung disease by HRCT,
- evidence of pulmonary function defects and
- histological examination of lung specimens demonstrating giant cell interstitial pneumonitis.

Flock worker's lung

- persistent respiratory symptoms;
- previous work in the flocking industry;
- histologic evidence of interstitial lung disease compatible with flock worker's disease

Asbestosis

- evidence of diffuse parenchymal lung disease either by HRCT or histology,
- evidence of a causal relationship by demonstrating environmental history of asbestos exposure with plausible latency,
- markers of exposure such as pleural plaques or recovery of asbestos bodies (BAL, lung specimen)
- exclusion of competing diagnoses.

Nanoparticle induced lung disease:

- 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.

A pivotal step in the diagnosis of CBD is the demonstration of beryllium sensitivity by beryllium-lymphocyte proliferation test (Be-LPT). At present Be-LPT with blood or bronchoalveolar lavage mononuclear cells is the only routine laboratory test available to prove beryllium hypersensitivity [37]. Skin tests such as patch test or intracutaneous tests should be avoided because there is a considerable risk of inducing sensitization by intra cutaneous application of beryllium salts and clear diagnostic readout criteria are not defined. Originally bronchoalveolar lavage cells have been employed in the Be-LPT [37] but for practicability reasons it has been adopted for the use of peripheral blood mononuclear cells [38]. Blood Be-LPT is used for diagnostic workup and occupational monitoring. Since Be-LPT is a biological ex-vivo test requiring viable cells usual quality standards of the clinical laboratory cannot be applied. The test should be performed in a laboratory with experience in cell biological testing and in some countries this test might not be available on a routine basis. 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.

To perform Be-LPT mononuclear cells have to be isolated from bronchoalveolar lavage or anti-coagulated (EDTA, heparin) peripheral venous blood. The latter one can be sent by overnight express to the laboratory but special containers and shipping conditions need to be employed which have to be tuned with the laboratory. For Be-LPT with bronchoalveolar lavage cells lavage needs to be performed at the site of the laboratory and to obtain sufficient numbers of cells larger volumes of 200 ml and more need to be installed. Cell culture without any additive is performed to estimate background proliferation and by addition of mitogens the viability

of the cells is demonstrated. The upper limit of background proliferation is laboratory dependent and needs to be individually established using mononuclear cells of unexposed controls. 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. In the authors laboratory 16 parallel cultures are used to establish background proliferation of patient and control cells. Cell cultures with different concentrations of BeSO4 over at least a three log-range between 10^{-4} and 10^{-6} mol/L are run in quadruplicate or more and proliferation is estimated once or several times between 3 and 8 days of culture. Tests with at least two elevated proliferation values are considered abnormal. Mitogen-induced proliferation serves as non-specific control [38, 39]. It has to be noted that outside the United States of America this test is not standardized and some laboratories use absolute numbers of stimulation indices as threshold or request dose-dependent proliferation for positive tests. As a consequence the clinician has to familiarize with the generation of the thresholds in the employed laboratory. Cell culture details of the test should be reported by the laboratory for correct interpretation of results. Since a specific positive control is not available, some authors demand two independent tests to accept the clinical consequence [40]. 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. Examples of positive and negative results from the laboratory of the authors are shown in Fig. 30.1.

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 % [39] and 100 % [38] with low interlaboratory reproducibility [41]. Consequently, there are cases of beryllosis 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 [38, 39, 42]. 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 [40]. In the 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 [37] (see Fig. 30.1). However, this can be markedly reduced by the effect of cigarette smoking causing a predominance of macrophages in the recovered cells potentially masking the lymphocyte response. Immunosuppresive compounds including steroids may dampen proliferation in response to beryllium and cause false negative results of Be-LPT. Although not systematically studied, most centers recommend discontinuation of steroid treatment for at least 3 weeks up to 3 months before Be-LPT is performed. However, own experience demonstrates that abnormal Be-LPTs can be obtained under low dose steroid treatment.

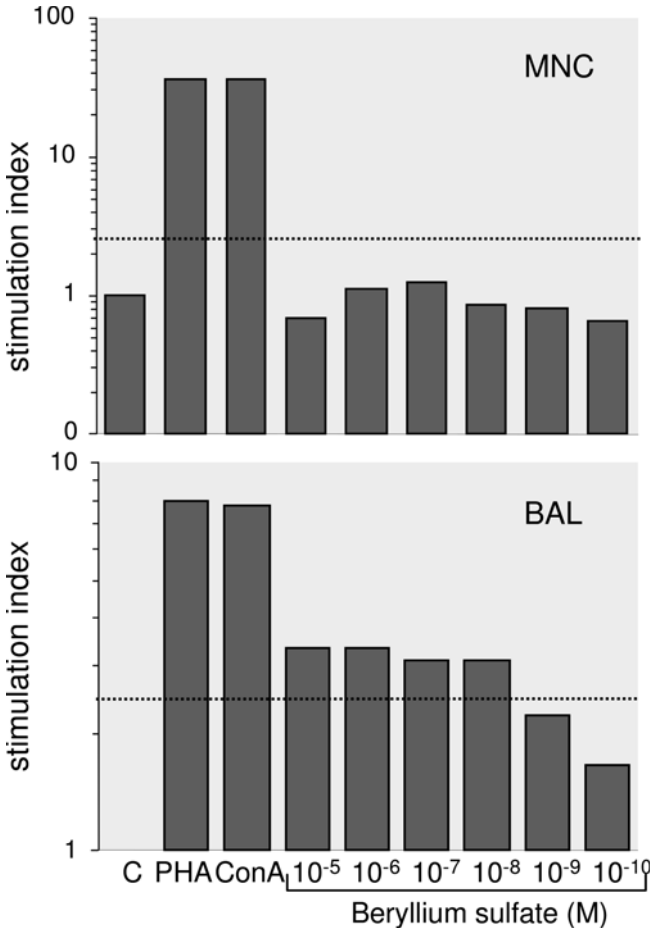

Fig. 30.1 Beryllium-lymphocyte proliferation tests with peripheral blood mononuclear cells (MNC, *top*) and bronchoalveolar lavage cells (BAL, *bottom*) of a patient with chronic beryllium disease are shown demonstrating the higher sensitivity of BeLPT using BAL-cells. The test with MNCs reveals a negative 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 [43]. Some beryllium exposed individuals have repeatedly

positive results demonstrating sensitization without pulmonary granulomas or other signs of disease. In a follow-up study 31 % of those individuals progressed to symptomatic CBD within 4 years [19]. 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 [44, 45], ELI-spot techniques [4, 46] 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 [47].

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 [25, 48–50].

Thus, for the unequivocal diagnosis of CBD the following criteria should be fulfilled:

- 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 the 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 [30]. 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.

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. Because CBD manifestation can take place a long time after exposure has ceased this should preferably be done with the help of an expert in occupational medicine which is, however, not practicable in most cases. Thus, a basic knowledge of beryllium usage is helpful to select patients to be referred to occupational medicine. Short or paraoccupational exposures may be missed without expert awareness of hazardous workplaces. Therefore, basic information on beryllium properties and uses in industries and technical trades is given in the following.

Beryllium is a metallic element found in beryl and bertrandite ores and processed into beryllium oxide, beryllium metal, beryllium alloys and composite materials. The mineral beryl is a beryllium aluminium cyclosilicate with the chemical formula $Be_3Al_2(SiO_3)_6$. Pure crystals of beryl are colorless and vary in size. Tinted with chrome they are green emeralds and tinted with iron or titan they are blue aquamarines. More than 80 % of the world's beryllium ore mining and processing is done in the United States. Kazakhstan and China are also beryllium producers. The most important product is copper alloy containing 0.15–2.0 % beryllium.

Copper-beryllium alloys withstand high temperatures and mechanical stress. They are extraordinarily hard but flexible, resistant to corrosion, do not spark, and are nonmagnetic. Beryllium and its alloys share a number of properties with aluminum, which explains their frequent use in aerospace and defense industry. Because the addition of beryllium improves the electrical and thermal conductivity of alloys, this metal is also frequently used in electronic and microelectronic applications such as semiconductor devices and integrated circuits requiring heat dissipation. Springs, switches, relays, and connectors in computers, radar, automobiles, telecommunication equipment, tools, and other instruments contain beryllium. Copper-beryllium is a common substrate for gold plated electrical connectors. Copper-beryllium scrap is often mingled with copper scrap for recycling. As a result, workers in both the metal recycling and precious metal recovery industries encounter beryllium.

Beryllium is used in casting of many different alloys where it refines the grain size resulting in better surface polishing, reduces melt losses, and improves casting fluidity. It also finds use as an acid catalyst in organic reactions, and as an additive to glass and plastics. Neutron moderators or reflectors in nuclear reactors and X-ray windows also contain beryllium. It is frequently found in gems and, depending on work processes, gem polishers are exposed. Jewelers may be exposed when precious stones are framed or polished. Optical crystals also contain beryllium; as a result beryllium-exposure takes place in the production of precision optical instruments including fiberoptics.

Beryllium oxide is the most important high-purity commercial beryllium chemical produced and its primary use is in the manufacturing of ceramics. Because beryllium-oxide is transparent to microwaves, it is also used in microwave devices.

Thus, the workers potentially exposed to beryllium are beryllium ore 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 workplace with implied beryllium exposure. Work places and their products with potential exposure are listed in Table 30.3.

Treatment and Monitoring

The first therapeutic measure is elimination of exposure and occupational studies reported reversibility of physiologic and radiographic defects when exposure is reduced or terminated [51, 52]. 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 [53]. 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 [54–56]. 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 [57]. Frequently recalcitrant disease can be suppressed with low dose corticosteroid maintenance therapy [57]. 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 [58, 59]. 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.

Table 30.3 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	Nonsparking tools	Wheels
Fluorescent lamp production/disposal	Nuclear reactors and industries	X-ray tubes
Gems	Optical industries/ workshops	

Prevention of Beryllium Sensitization and Chronic Beryllium Disease

After diagnosing CBD competent 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 [60]. 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 [40, 61, 62].

Although genetic factors determining susceptibility for beryllium sensitization and the risk for progression to CBD are known [14] 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 [53]. 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 [53]. 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 [14, 53].

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 intraalveolar particles by energy dispersive X-ray analysis of a patient suffering from interstitial lung disease. Physical examination disclosed clubbing and fine crackles with high pitched squeaks on auscultation. Chest CT-scan showed ground glass opacities all over the lung and subpleural honeycombing. Exposure time was 3 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 [63]. More cases with interstitial pneumonitis, pulmonary fibrosis, and emphysematous defects have been reported in smoking and non-smoking workers from Japan and a causal dose-dependent relationships between ITO-exposure and interstitial and/or emphysematous defects in CT-scans and serum level of KL-6, SP-A and SP-D could be established in a large cross-sectional study with 592 ITO exposed workers in Japan [64, 65] and in 170 workers in Taiwan [66].

Two cases of pulmonary alveolar proteinosis (PAP), including one death, were observed in workers at a facility in the United States of America producing ITO. In one antibodies against granulocyte-macrophage colony stimulating factor (GM-CSF) could be identified suggesting an immunologic mechanism induced by ITO [67]. However, anti GM-CSF could not be found in 17 ITO workers in Japan but reevaluation of Japanese cases demonstrated next to cholesterol clefts periodic acid Schiff (PAS)-positive material in the alveolar space of 4 out of 7 cases [68]. PAS material could also be generated by toxic effects of ITO on alveolar macrophages as shown in an animal study [69]. In aggregate, the observations are compatible with PAP and PAS-positive material in the alveolar space as an acute ITO response which is replaced by cholesterol clefts and fibrosis in the long term [68].

In a study of 108 male ITO workers in the facility in which the first case of ITO-lung disease was observed in 23 workers disclosed significant reticulonodular shadows on HRCT of the chest. In addition, in 14 of those 23 workers emphysematous changes could be seen. These radiographic changes correlated with both the serological marker of alveolitis KL-6 and the length of exposure [65].

As for CBD a suspicion of ITO-lung disease can only arise when a compatible clinical appearance combines with an occupational exposure. Clinical clues for ITO-lung disease can be:

- Reticular nodular shadows with fibrosis and cholesterol clefts ± emphysematous lesions
- Pulmonary alveolar proteinosis without or only moderate concentration of GM-CSF autoantibodies.

Generally accepted therapeutic recommendations do not exist. Terminating exposure has lead to complete recovery [70]. The value of therapeutic bronchoalveolar lavage or corticosteroid therapy needs to be established [67].

CBD is an exposure-related form of sarcoidosis and alike ITO-lung disease might turn out to be an exposure-related form of PAP or pulmonary fibrosis with emphysema. The relevance of anti-GM-CSF antibodies and elevated serum markers, as KL-6, SP-A or SP-D, in pathogenesis and disease managing has still to be established.

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 which is blended with 6–10 % cobalt as a binder and compressed into a polycrystalline material [71, 72]. 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 [71–73]. Workers exposed to hard metals are toolmakers, blacksmiths, diamond polisher and workers processing steel alloys containing hard metal [71, 74]. 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 [75]. Later, Ohori and colleagues confirmed the finding that GIP is almost pathognomonic for hard metal or cobalt exposure [76]. However, not every case of hard metal lung disease appears as GIP. Other types of interstitial pneumonia were also documented to be manifestations of hard metal lung disease such as DIP, UIP and BOOP [76]. The presence of multinucleated giant cells can be easily documented by BAL, which can also be used for mineral analysis and detection of tungsten.

Animal experiments and case reports suggest that cobalt is the key agent inducing ILD by hard metal [77–80]. However, Lison and colleagues reported that cobalt bound in hard metal is more toxic than in other compounds indicating that cobalt alone cannot be responsible for the toxicity of hard metal particles [81].

In our outpatient clinic we established the diagnosis of giant cell interstitial pneumonia (GIP) in an 82 year old, never-smoking, retired lady. HRCT revealed subpleural honeycombing combined with diffuse ground glass lesions (Fig. 30.2). She worked for 20 years in a spinning mill and was exposed to cobalt containing paints which lead to the diagnosis of occupational hard metal lung was made. An example of giant cell pneumonitis is shown in Fig. 30.3.

In contrast to pneumoconiosis, a dose-response relationship is not evident in hard metal lung disease. Evidence suggests a delayed-type hypersensitivity immune response to be involved and clinical characteristics are often similar to hypersensitivity pneumonitis [82, 83]. 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 [74, 82, 84, 85].

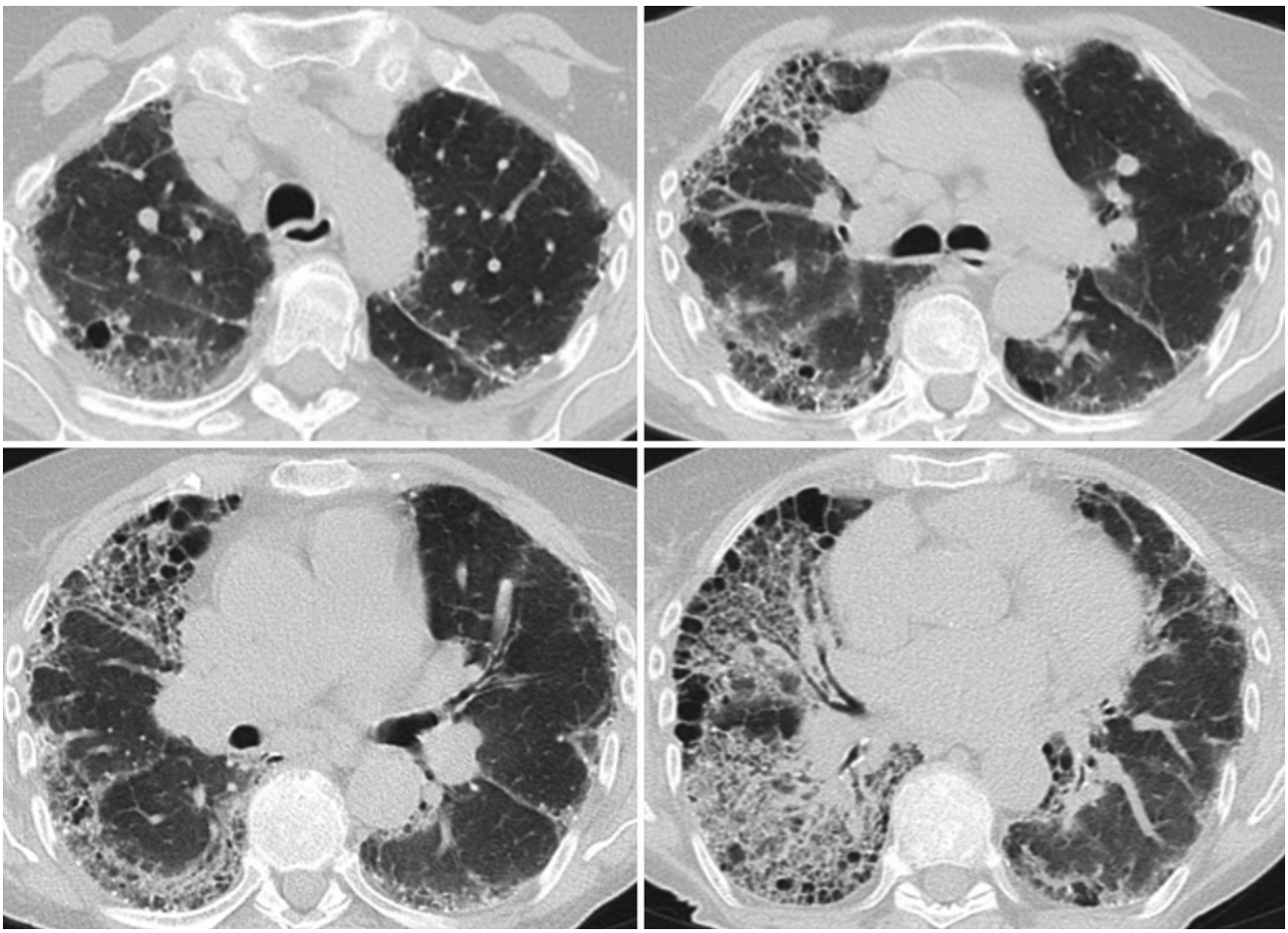

Fig. 30.2 HRCT scan of a 82 year old patient with giant cell interstitial pneumonitis after Cobalt exposure at yarn factory. Histological diagnosis was obtained by transbronchial biopsy and confirmed by wedge biopsy. HRCT shows diffuse severe lesions, predominately in the right lung. There is severe subpleural honeycombing on both sides. Beside 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

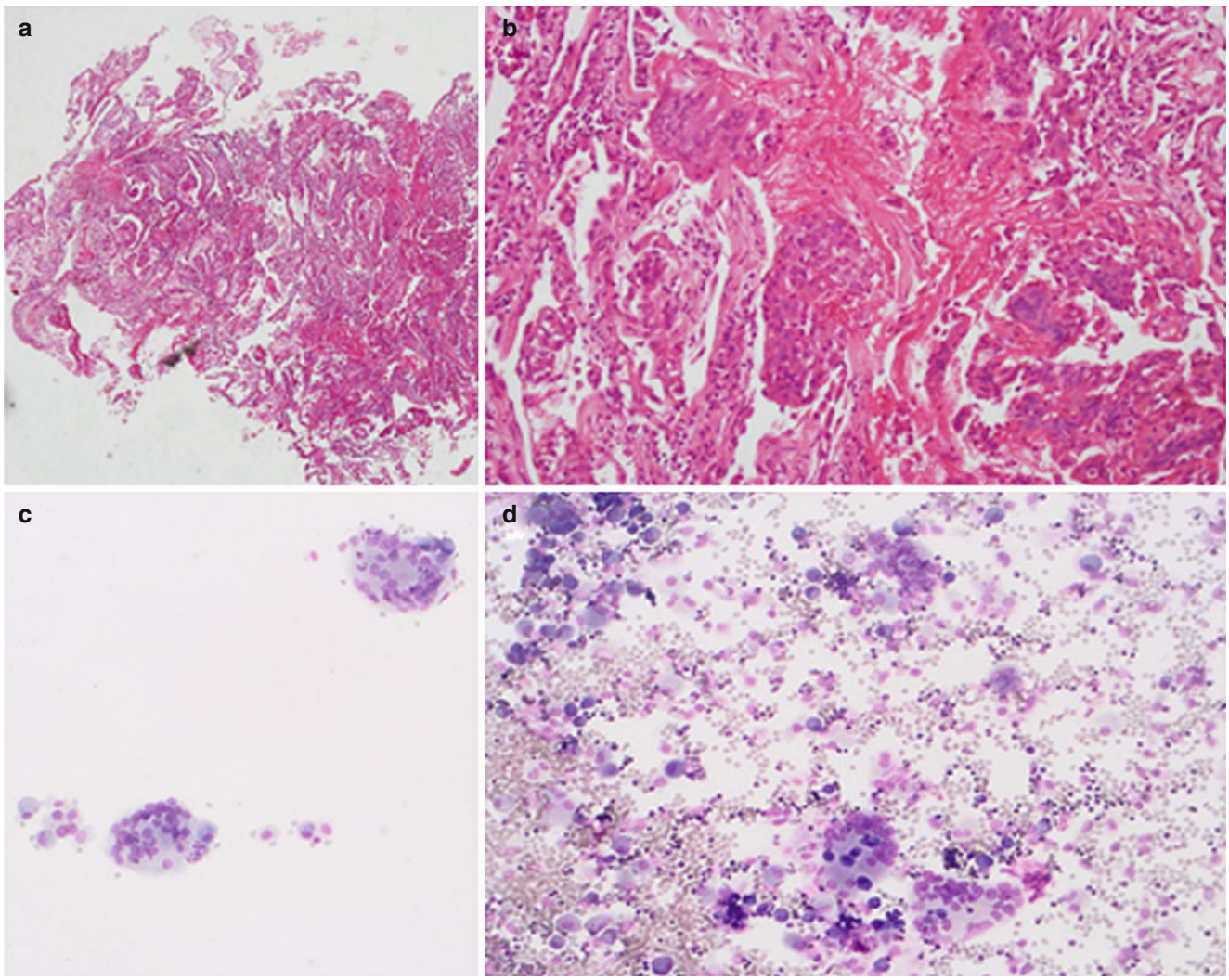

Fig. 30.3 Depicted are a transbronchial biopsy and a BAL cytology of a 82 year old lady with giant cell interstitial pneumonitis. Panels **a** and **b**: transbronchial biopsy and panels **c** and **d**: BAL both with giant cells

Unfortunately, criteria for the diagnosis of hard metal induced lung disease which are generally agreed on are missing. Thus, in view of the literature [86, 87] 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.

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 [88]. The diameter of the fibers ranges from 0.3 to 2.0 mm [89]. However, depending on the cutting process very small, respirable fibers might be generated [90]. First reports described ILDs in textile workers [91, 92]. The term flock worker`s disease was introduced 1998 by Kern and colleagues [90] 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. However, 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 [93–95]. Noteworthy, granuloma formation has not been described [94, 95]. Often an increase in lymphocytes can 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 [90, 96, 97]. The acute type of the disease can be associated with fever, fatigue, and weight loss. However, a substantial number of patients progress and require long-term oxygen treatment [93].

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. 30.4) and histology of wedge biopsy were consistent with non-specific interstitial pneumonia (NSIP, Fig. 30.5). High dose prednisolone treatment did not show any effect and 8 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. Of interest, a majority of the patients will develop a relapse after re-exposure [93]. 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 [93, 98].

Patients with strong suspicion of flock workers 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 [88, 99].

There are no studies evaluating immunosuppressive treatment in flock worker`s disease [93, 98]. 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 [100]. 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. The most commonly used chrysotile is a serpentine fiber and less toxic than amphiboles [101–103]. 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 [104]. It is well established that there is a dose response relationship between pulmonary lesions and asbestos exposure [105–107]. The cumulative pulmonary burden is crucial for disease development. Cigarette smoking by interfering with mucociliary clearance increases cumulative burden and aggravates asbestos induced pulmonary diseases [108]. Very common are pleural lesions caused by asbestos exposure and pleural plaques are considered as pathognomonic for asbestos exposure [100, 109].

There is a latency period of about 15–30 years between exposure to asbestos and development of asbestosis [101, 110]. Asbestos is of cellular toxicity and deposited in the respiratory bronchiole where it is phagocytosed by alveolar macrophages and alveolar epithelial cells [111]. Alveolar macrophages transport fibers to the pleura via lymphatics. Multiple evidence derived from animal experiments documents dose-dependent asbestos induced pulmonary inflammation and fibrosis [112, 113]. 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 [114, 115]. Noteworthy, inflammasome activation results in pulmonary fibrosis [116]. 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 [117] has developed histologic criteria for asbestosis and a grading system (I–VI). Alveolar collapse and honeycomb remodeling is the most severe grade (VI). 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 [118]. 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 [119]. Typical changes are also pleural plaques, pleural thickening, rounded atelectasis, parenchymal bands and curvilinear lines [120–122] (Fig. 30.6).

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,

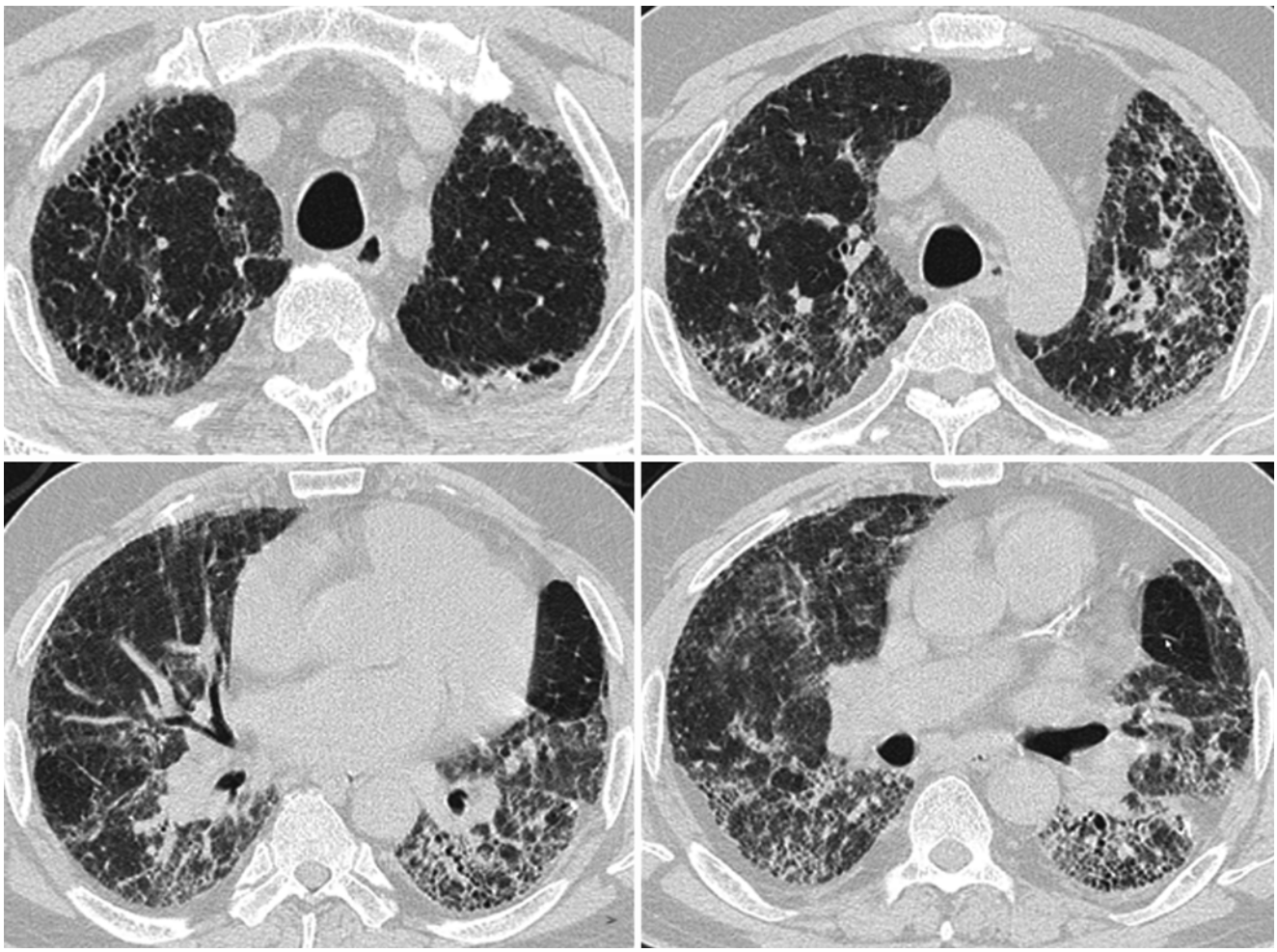

Fig. 30.4 HRCT scan of a 58 year old patient with severe, subacute flock worker`s disease after exposure in a filter factory. Patient died because of acute exacerbation. HRCT shows severe diffuse ground glass lesions in both lungs and reticular bands. There is also some honeycombing in the lower subpleural regions and considerable pleural thickening

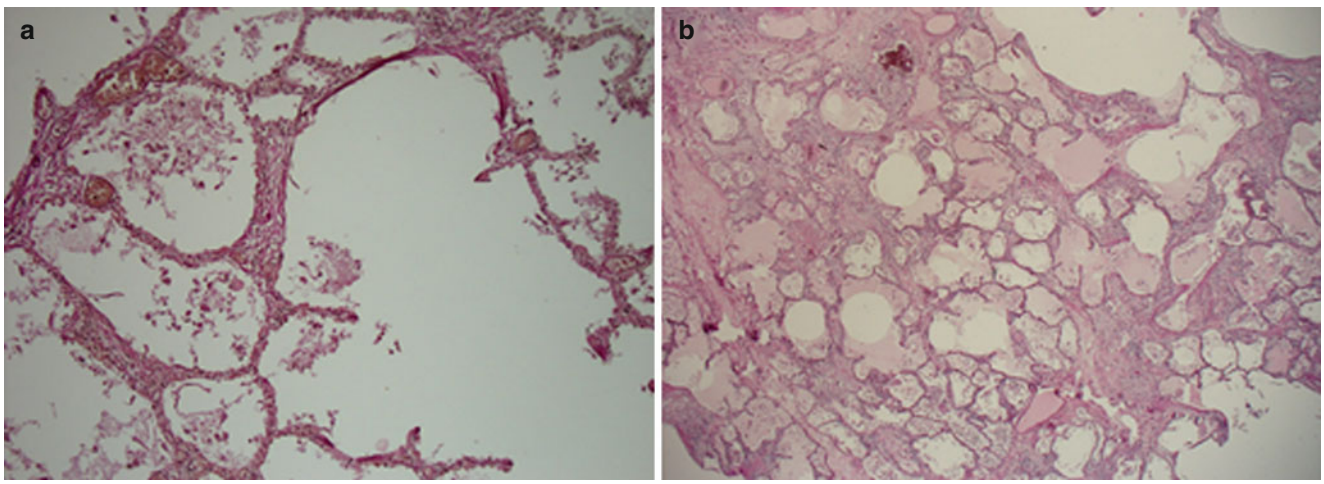

Fig. 30.5 Microphotographs from the lungs of the 58 year old patient with flock worker's disease who died because of acute exacerbation. Panel **a** and **b**: Autopsy revealed morphology predominately consistent with NSIP and diffuse alveolar damage. Intraalveolar edema and alveolar desquamation is due to respiratory failure and subsequent death

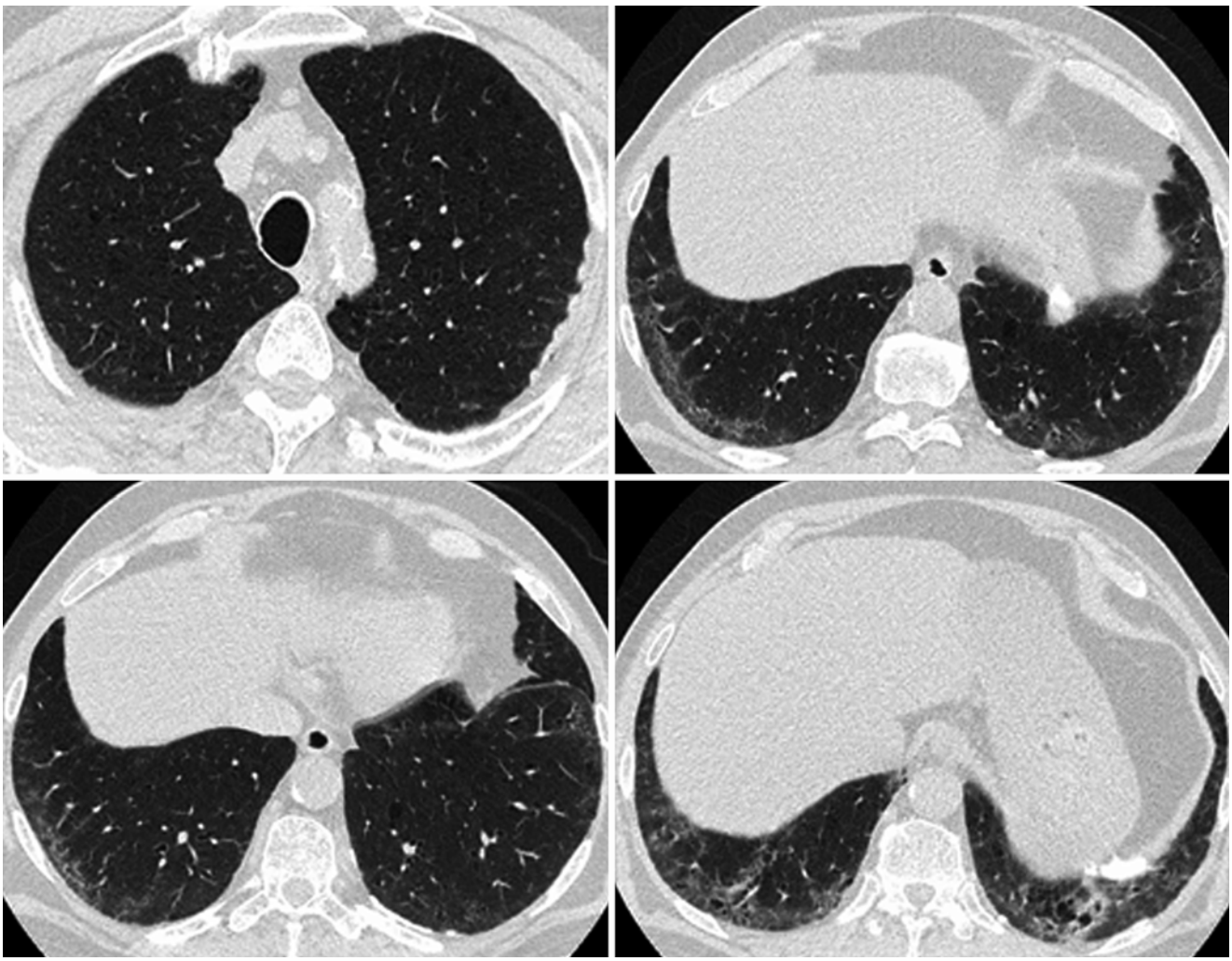

Fig. 30.6 HRCT scan of a 62 year old plumber with asbestosis showing linear opacities and subpleural nodular opacities (*upper left*), ground-glass attenuation, subpleural honeycombing, and calcified plaques

- markers of exposure such as pleural plaques or recovery of asbestos bodies (BAL, lung specimen) [100, 123–126] (Fig. 30.7) and
- exclusion of competing diagnoses.

Patients 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 [127].

In some patients asbestosis progresses rapidly, while in others the disease may be stable over years. Co-factors of progression have not yet been identified but total lung burden seems to be the most important determinant of disease progression.

There is no evidence based approach for treatment of asbestosis [128]. 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 [100].

Nanoparticle Induced ILD

Nanoparticles are defined as particles sized [129] between 100 and 1 nm. There is a huge variety of nanoparticles which can be composed of various organic and an organic substances. They are generated by combustion processes such as diesel exhaust or by any process burning fuel such as welding. Worldwide man-made nanostructures are used in multiple and increasing application areas.

Several studies have shown that particle size has tremendous 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 [130, 131]. In addition,

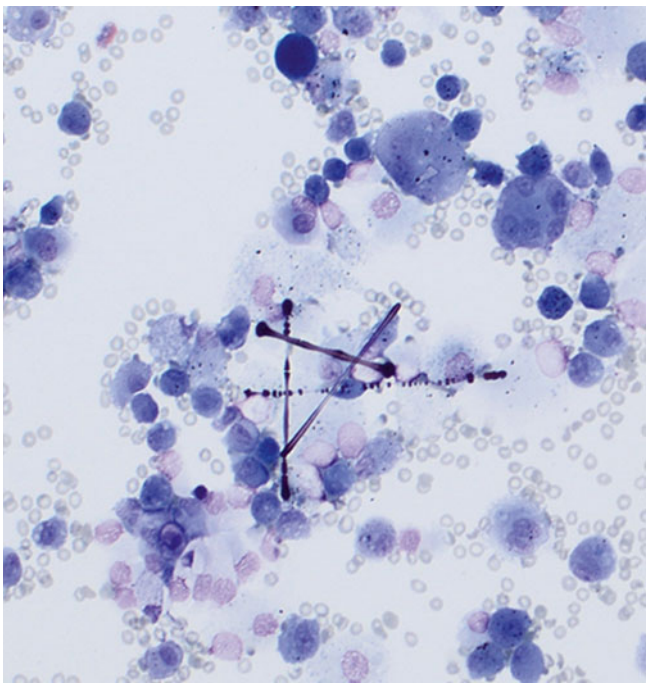

Fig. 30.7 BAL cytospin of a 62 year old plumber with asbestosis showing 4 asbestos fibres

nanoparticles often contain metals which can further enhance their toxicity. Because of the wide spectrum of nanoparticles there is no uniform pulmonary toxicity and each nanostructure might cause different pulmonary lesions. 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 [129, 132]. Moreover, single wall carbon nanotubes seem to be more toxic than quartz [132]. Bonner and colleagues showed that vanadium pentoxide induces pulmonary fibrosis in rats [133]. Furthermore, 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 [134, 135]. 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 very limited so far. Song and colleagues [136] described 7 female workers exposed to spray paint under extreme working conditions without any exhaust. 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. However, the authors failed to demonstrate data regarding the type and dose of nanoparticles and possible other substances [136, 137]. 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. To our knowledge no other report has been published which documents nanoparticle induced ILD in humans so far.

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 gauge 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 toxilogical response to nanoparticles are not known [138, 139]. Nevertheless, current knowledge suggests that 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 [87, 118, 140].

Conclusion

With the enforcement of higher safety standards at the workplace in industrialized nations the frequency of classical occupational interstitial lung diseases is going down but new emerge such as flock worker's disease which has been recognized only 20 years ago. Nevertheless, diagnostic awareness in the diagnostic workup of interstitial lung diseases needs to be high since hazards previously thought to be only important for the worker may be of relevance for bystanders and the worker's family. Such bystander and paraoccupational diseases are most frequently caused by the transport of hazardous material in the clothes of workers to other places and the home. Outbreaks of paraoccupational diseases caused by beryllium, asbestos, and other compounds have been traced to contamination by industrial dust [11]. 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 disease which can only be achieved by a high vigilance of medical professionals.

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Lymphoproliferative Lung Disorders

31

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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 31.1). The natural history of many of the conditions is variable with further heterogeneity recognised within distinct disease entities. Primary pulmonary lymphoproliferative diseases are rare, whereas secondary pulmonary lymphomas occurs in up to 20.5 % of autopsy cases. The lung is a potential organ for tumour 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 clinico-pathological patterns: intrapulmonary lymph nodes, nodular lymphoid hyperplasia, follicular bronchitis/bronchiolitis, lymphocytic interstitial pneumonia (LIP) and Castelman's disease.

Malignant lymphoproliferative diseases are distinguished in Hodgkin's and non-Hodgkin's lymphomas (HL and NHL), affecting B or T/NK cells. Malignant lymphoproliferative disorders may arise 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 or from neighbouring sites (e.g. from mediastinal lymph nodes or thymus).

Malignant proliferative diseases occur more frequently in immunocompromised hosts, having in post-transplantated and in HIV ± patients a slightly different clinical and pathological profile from patients with autoimmune disorders or immune competent hosts.

Reactive Pulmonary Lymphoproliferative Disease

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 intraparenchimal lymph nodes high-resolution computed tomography (HRCT), positron emission computed tomography (PET-CT) are useful tools, but surgery is necessary to obtain a definitive diagnosis.

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Table 31.1 Classification of primary pulmonary lymphoproliferative diseases

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…) Immunodeficiency (familial, common variable immunodeficiency, HIV…) Dyspnea on effort, bronchorrhea Obstructive impairment Lymphoid follicles (B cells) around bronchioles	Small nodules (centrilobular/ broncocentric) bronchial wall thickening	Surgical biopsy (BAL is an ancillary test)	Macrolides Steroids
LIP	Background of autoimmunity (Sjogren….) Dyspnea on effort, cough Restrictive impairment Diffuse interalveolar infiltration of lymphocytes (CD3+cells), lymphoid hyperplasia (follicles consisting of B cells around bronchioles) scattered granulomas	Centrilobular nodules, septal thickening, ground glass attenuation, cysts	Surgical lung biopsy	Steroids (BAL is an ancillary test; Azathiprine immunohistochemistry/ Cyclophosph.. molecular tests to exclude a monoclonal component)
MALT Lymphoma	Mean age 60 yrs Asymptomatic (minority of cases) B symptoms (fever, asthenia,…) in a minority of cases) Respiratory symptoms (cough, dyspnea Autoimmune background (Sjogren..) as a predisponent condition 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	Rounded or segmental shaped consolidations Air bronchogram Ground glass opacities Hilar/ mediastinal lymphnodes Reticular, perilymphatic opacities	Surgical biopsy CT scan guided or TBB biopsy BAL	Chemotherapy Rituximab
T cell rich B cell Lymphoma (LYG)	Respiratory symptoms (cough, dyspnea, chest pain, acute respiratory failure) Systemic manifestations (fever, malaise, weight loss) 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	Multiple nodules Diffuse reticulonodular infiltrates (rare) Cavitation (10–25 %)	Surgical Biopsy	Chemotherapy Rituximab

Intravascular B cell Lymphoma	Occurs in older patients Dyspnea; pulmonary hypertension; clinical onset mimicking pulmonary thromboembolism Systemic symptoms (fever…) Symptoms manifesting an extrapulmonary involvement (CNS, skin…) Important reduction of PAO2 and PaCO2 inspite 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 "intersdtitial pneumonitis" or "minimal changes"	Peripheral wedge shaped lesions; pleural effusion (bilateral); mosaic oligoemia; normal CT aspects/diffuse pulmonary uptake on FDG-PET	Surgical Biopsy TBB biopsy	Chemotherapy Rituximab
Extra-nasal-type NK/T cell Lymphoma	Systemic symptoms (fever, malaise, weight loss) Respiratory symptoms (dyspnea, cough, acute respiratory failure) Extrapulmonary involvement Skin,…) An opportunistic infection may be the first clinical manifestation Marked lymphopenia (CD4+cells); elevated LDH; hemophagocytic syndrome 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 in the majority of cases	Nodules or masses (possibly escavated) Superimposed infections manifesting with ground glass attenuation or "crazy paving"	Surgical biopsy TBB biopsy	Chemotherapy

Reactive pulmonary lymphoid hyperplasia includes nodular lymphoid hyperplasia and diffuse lymphoid hyperplasia, this last one encompassing the two histological patterns of lymphocytic interstitial pneumonia (LIP), follicular bronchitis/bronchiolitis and Castleman's disease (CD).

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 years prior to presentation. He reported no exposure to tuberculosis and tuberculosis skin test was negative. In the past he suffered from malaria. Laboratory tests revealed anemia (Hb 6.5 g/dl), elevated C reactive protein (CRP), monoclonal hyperimmunoglobulinemia IgG Kappa, and an elevated interleukin-6 level: 37, (normal value <11). A contrast enhanced CT of the chest and abdomen showed ground glass opacities and interlobular septal thickenings in the lungs (Fig. 31.1) accompanied with axillary, hilar, mediastinal and abdominal lymphadenopathies with hepatosplenomegaly. Rigid broncoschopy was performed for transbronchial needle aspiration in sub carinal lymph node and transbronchial lung biopsy. Plasmacytic infiltration of the lymphoid tissue with scattered lymphoid CD30 positive cells with a blastoid morphoplogy and plasmacytic and lymphocytic infiltration in the pulmonary interalveolar septa and around the bronchovascular bundles were documented. In situ hibrydization using probes to detect the Human Herpesvirus 8 (HHV-8) particles revealed positive cells in the lung parenchyma.

To confirm the diagnosis, of Castleman disease an excision biopsy of axillary nodes was performed. Interfollicular expansion composed predominantly of plasma cells with some degree of atypia associated with follicular hyperplasia was documented, suggesting HHV-8 correlated multicentric Castleman's disease, plasma cell type (Fig. 31.2a, b).

After chemotherapy, the symptoms that included fever and sweating subsided.

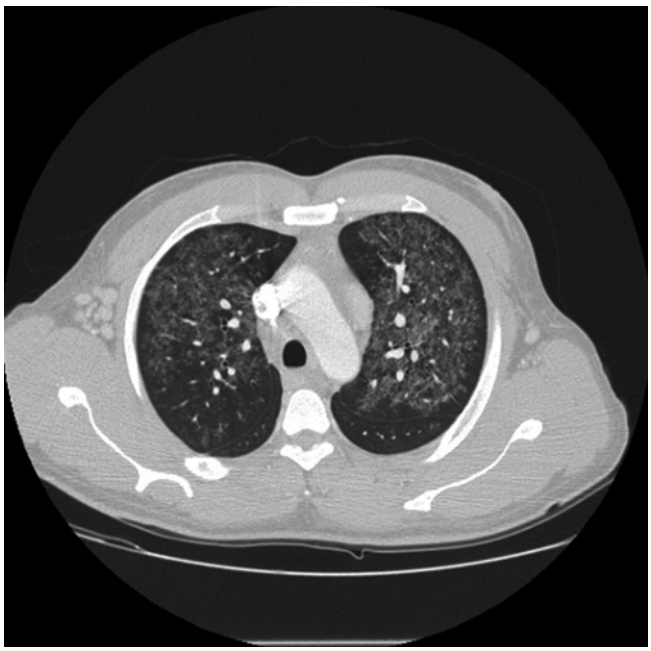

Fig. 31.1 Lung window of the contrast-enhanced CT scan of the chest. Multiple centrilobular ground glass opacities are present in both upper lobes. A relative subpleural sparing and mild septal thickening are also present

Castleman's Disease

Castleman's disease is an uncommon clinicopathological entity first described in 1956 [1]. The incidence is not known and can occur at any age, though it has mostly been

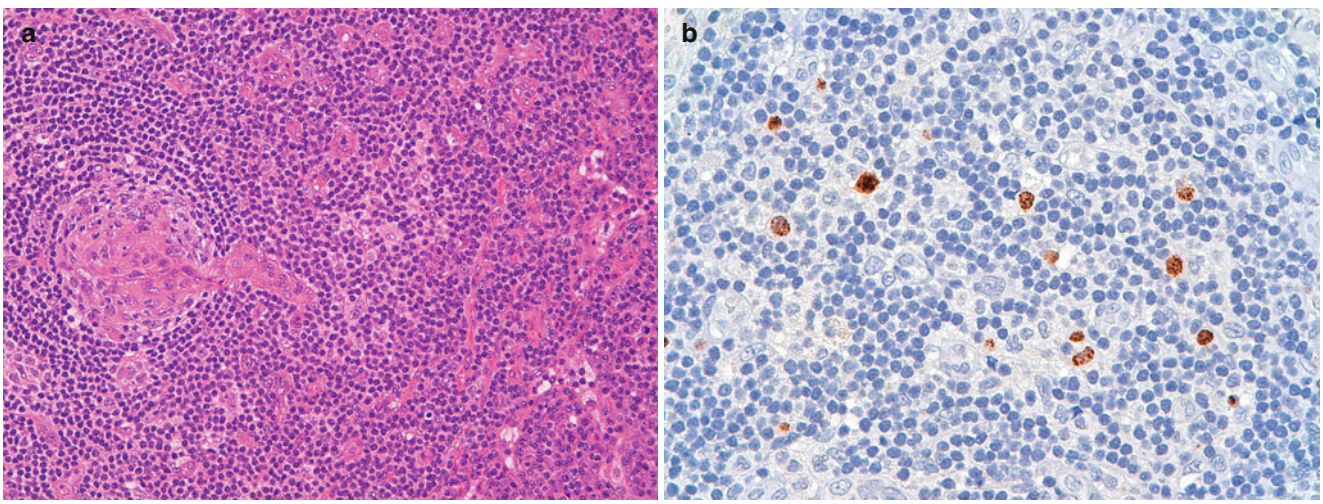

Fig. 31.2 (**a**, **b**) Histological finding of axillary nodes biopsy: (**a**) A burn out follicle with a prominent, hyalinized penetrating blood vessel (lollipop appearance); characteristic "onion skin" appearance due to the lamination of the mantle cell layers. (**b**) Focal immunoreactivity for HHV8 Interfollicular expansion composed predominantly of plasma cells and some degree of atypia associated with follicular hyperplasia

reported in adults in the literature. CD is classified according to the clinical and the histopathologic profile, as localized (hyaline- vascular, plasma-cell type) or multicentric with histologic features of one or both of the localized types [2, 3]. The hyaline- vascular type (HV) shows numerous follicles with around a concentric layering of B small lymphocytes (CD20+, IgD+) in an onion-skin apparence, depleted, abnormal, germinal center (CD20+, Bcl6+, Bcl2−) with penetrating hyalinized capillaries in "lollipop" apparence, and large dysplastic cells with vescicular nuclei consistent with follicular dentritic cells (CD21+, CD23+, CD35+). Actually, it has been recognized that CD represent a neoplasm of follicular dentritic cells because have been reported clonal cytogenetic abnormalities in FDC cells [4]. The interfollicular stroma shows marked vascular proliferation, polyclonal plasma cells, immunoblasts, plasmacytoid dentritic cells (CD123+, CD68+,) and myoid cells. Cases of CD in wich the myoid cells are prominent have been referred to as stroma-rich variant of hyaline-vascular CD [5].

The plasma cells type (PC) is characterized by a diffuse polytypic or monotypic (IgA lambda) plasma cells proliferation, often in sheets, in the interfollicular stroma.

The localized form of the disease is mostly asymptomatic with a single site lymph node enlargement. The sites commonly involved are abdomen, peripheral lymph nodes and the mediastinum. It is often discovered incidentally during routine examination, chest X rays. Diagnosis is made by histological analysis of the lymph node biopsy to distinguish it from a thymoma. Multifocal CD, however, presents with systemic symptoms along with multiple lymph node hyperplasia.

Interest in multicentric (M-CD) has grown following the observation that this pathology is often associated with human immunodeficiency virus (HIV) infection and with (*HHV8*, or Kaposi's sarcoma *herpesvirus* KSHV) and *Epstein Barr virus* (EBV) infections [6]. Pathogenesis remain largely unknown, but *HHV8* and *Epstein Barr* virus may encodes for an homologue of interleukin 6 (vIL 6) which may mediate some systemic features of MCD. Multicentric CD in HIV + patients have a higher prevalence of pulmonary symptoms and usually present with generalized lymphadenopathy characterised by perifollicular vascular proliferation and germinal center angiosclerosis, polyclonal hypergammaglobulinemia, hepatosplenomegaly and constitutional symptoms.

In immunocompetent host the more common pattern is the hyaline-vascular, the associated clinical type is usually the localised one, an asymptomatic mediastinal mass quite benign because in most cases curable by surgery. The plasma-cell variant is more often associated with the multicentric disease characterized by lymphadenopathy, hepatosplenomegaly, skin rashes, sweating, fatigue, anaemia, elevated erythrocyte sedimentation rate (ESR), polyclonal hypergammaglobulinemia and bone-marrow plasmacytosis. It may be associated with the POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M-proteins and skin changes). The systemic symptoms are thought to be primarily a consequence of elevated Interleukin-6 (IL-6) production [7, 8]. Recently, a unique clinicopathologic variant of multicentric Castleman's disease (MCD) called TAFRO (thrombocytopenia, anasarca, fever, reticulin fibrosis and organomegaly) has been identified in Japan. This disease is characterized by a constellation of symptoms, as listed above, and multiple lymphadenopathy of mild degree with a pathologic diagnosis of atypical CD, often posing diagnostic and therapeutic problems for pathologists and hematologists, respectively. These findings suggest that this disease represents a novel clinical entity belonging to systemic inflammatory disorders with a background of immunological abnormality beyond the ordinal spectrum of MCD [9].

Clinical manifestations of lung involvement include dyspnoea, cough, bilateral crackles, or rapidly progressive respiratory failure. Pulmonary symptoms develop always simultaneously with severe systemic manifestations: high grade fever, malaise, generalised lymphadenopathy and hepatosplenomegaly. Hypoxaemia and hypocapnia are often present.

Chest radiographs show reticular and/or nodular interstitial patterns often associated with mediastinal lymphadenopathy and in some cases accompanied by bilateral pleural effusions. Common CT findings are poorly defined centrilobular nodules, thickening of the bronchovascular bundles and interlobular septae, and thin-walled cysts, mostly related to diffuse interstitial, interalveolar, infiltration of small lymphocytes (LIP pattern). Less common findings include subpleural nodules, areas of ground glass attenuation air-space consolidation and bronchiectasis. Bronchoscopy is usually negative, BAL hypercellularity mainly due to an increase of CD8 + lymphocytes is usually present but it is not specific. Microbiological investigations on BAL fluid permit to exclude common infectious aetiologies, and genotyping analysis allows to detect HHV-8 DNA. Definite diagnosis is histological, most cases being diagnosed by peripheral lymph-node biopsy. Specimens of pulmonary lesions may be obtained by trans-bronchial biopsy or by surgical biopsy. Localized CD usually has a good prognosis and requires surgical excision of the enlarged lymph node with no further treatment. M-CD however tends to have a variable prognosis with no documented treatment consensus [2, 3]. Median survival in HIV + patients is 14 months, patients die of infections, transformation to NHL (Large B cell lymphoma associated M-CD or Plasmablastic lymphoma) or chemotherapy toxicity. A variety of combination treatments have been tried with surgical excision, chemotherapy and steroids. In patients with associated Kaposi's sarcoma polychemotherapy (e.g. cyclophosphamide, vincristine, doxorubicin and prednisone) has been tried with limited success. First line treatment of M-CD in non HIV patients consist of single chemotherapeutic agent, high doses of steroid and/or anti CD-20 monoclonal antibodies. Studies show that

humanized anti-human interleukin-6 receptor monoclonal antibody significantly alleviate chronic inflammatory symptoms and wasting [10, 11]. Systemic and pulmonary symptoms improve more rapidly and may disappear. Recently it has been demonstrated that the M-CD symptoms improved by treatment with tocilizumab, which is a humanised antihuman IL-6 receptor monoclonal antibody and corticosteroid [12]. Complete resolution of TAFRO syndrome after immunosuppressive therapies using corticosteroids and cyclosporin A has been reported [13]. However prognosis remain poor, patients die after relapsing of disease, progression to lymphoma or for bacterial sepsis, median survival time being 5 years. Finally treatment with the antiherpesvirus drug, gangciclovir alone or with the antiCD20 B cell monoclonal antibody, rituximab, may markedly improve outcome.

Nodular Lymphoid Hyperplasia

Nodular lymphoid hyperplasia, also known as "pseudolymphoma", is a localized mass characterized by a lymphoid infiltrate with a lack of evidence of clonality despite immunohistochemical and genetic studies. The most common clinico-radiological feature is a localized and asymptomatic mass, although few patients present fever and elevated ESR. The single lesion is usually curable by surgical excision. Finally it is needed to evaluate the possibility of nodular lymphoid hyperplasia (pseudolymphoma) or clonal lymphoproliferative disorder in the lung as potential manifestations of immunoglobulin(Ig)G4-related disease [14, 15].

Lymphocytic Interstitial Pneumonia (LIP)

Lymphocytic interstitial pneumonia (LIP) [16, 17] is a rare interstitial lung disease characterized by the presence of aggregates of B and T reactive lymphocytes within the lung interstitium.

LIP is associated with serum protein abnormality (monoclonal gammopathy, polyclonal dysproteinemia, hypogammaglobulinemia), immunological disorders, such as Sjogren syndrome (25 % of cases), primary biliary cirrhosis, myasthenia gravis, Hashimoto thyroiditis, pernicious anemia/agammaglobulinemia, autoimmune haemolytic anemia, systemic lupus erythematosus, celiac disease, *HIV infection*, *EBV infection*, *chronic active hepatitis*, other infections (e.g., *pneumocystis*, *tuberculosis*), drug injury, allogeneic bone marrow transplantation (GVHD), extrinsic allergic alveolitis. LIP occurs more commonly in women and the mean age is around 55 years.

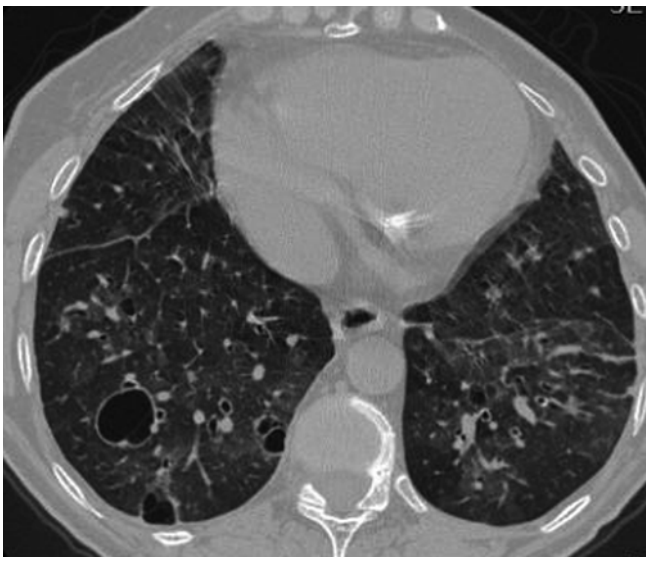

Fig. 31.3 CT scan shows bilateral areas of ground glass attenuation, with a pathcy distribution. Some cyst, variable in size are present in both lower lobes, mainly on the right side. Mild interlobular septal thickening is also present. Findings are consistent with LIP

Presenting symptoms are progressive cough and dyspnoea, weight loss, fever, 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 centrolobular 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. 31.3), and lymph node enlargement (68 %). Less common findings include nodules 1–2 cm in diameter (41 %), airspace consolidation (41 %), emphysema (23 %), bronchiectasis (18 %), pleural thickening (18 %), and honeycombing (5 %). Honeycombing and pulmonary hypertension appears in advanced disease. Pleural effusion are 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 sometimes noted. Intraalveolar accumulation of small lymphocytes, scanty granulation tissue tufts, and proteinaceous material along with type II cell hyperplasia are ancillary

findings. Immunohistochemestry using CD20 shows that B cells are mainly limited to germinal centres (CD10+, Bcl6+, Bcl2−). The interstitial, interalveolar, lymphocytes are prominently T-cells, while the follicles are mainly constituited by B lymphocytes. The immunoglobulin heavy chain gene or the T cell receptor gene using the polymerase chain reaction show no rearrangement. *Epstein-Barr virus* has been identified in lung biopsy specimens from both HIV infected and non-infected patients [18, 19].

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 due to progression to fibrosis, *cor pulmonale* and respiratory failure, to superimposed infection, or to development of a complicating lymphoma.

Follicular Bronchitis/Bronchiolitis

Follicular bronchitis/bronchiolitis is a term introduced to describe the predominant peribronchial lymphocytic infiltrate with abundant germinal centres, often associated with various allergic diathesis, immunodeficiency disorders (*HIV infection*, common immunodeficiency syndromes), and collagen vascular diseases.

Patients usually present dyspnoea, occasionally fever and cough, hypoxemia, hypocapnia; either obstructive or restrictive spirometric patterns have been reported. The chest film shows bilateral reticular or nodular opacity. Common high-resolution CT findings are centrolobular nodules, bronchiolar dilatation, tree in bud and mosaic perfusion patterns. Expiratory dynamic HRCT scans are important to assess air trapping. Flow-cytometry of BAL usually document a slight increase of polyclonal B lymphocytes. Surgical lung biopsy is often performed to obtain a definite histological diagnosis. Therapy with steroids and also with macrolides at low dose may have some benefit.

Primary Pulmonary Lymphomas

Primary Pulmonary Lymphomas (PPL) are 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 tumours of lung (WHO 2004) classifies PPL into B-cell primary pulmonary NHL, as 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 be the primary site of presentation of most type of nodal lymphoma (WHO Classification 2008) such as Follicular lymphoma (FL), Mantle cell lymphoma (MCL), extraosseous plasmacytoma (EP), Intravascular large B cell lymphoma (IVLBCL), Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease, Plasmablastic lymphoma (PBL), T/NK lymphoma, Anaplastic large-cell lymphoma (ALCL), and Hodgkin lymphoma (HD).

Primary pulmonary non Hodgkin's lymphoma (NHL) is very rare and accounts 0.4 % of all lymphomas and 3.6 % of extranodal lymphoma. Mature B-cell neoplasmas are the prevalent fenotype.

B-Cell Non-Hodgkin Lymphomas

The most common histotype is mucosa-associated lymphoid tissue type (MALT) B cell lymphoma, which represents 70–90 % of all primary pulmonary NHL [16–21]. Diffuse large B cell lymphoma (DLBCL) occurs only in 10 % cases of primary pulmonary NHL [21]. In some cases, transformation from MALT lymphoma to DLBCL may occur. Clinically, these present with non-specific symptoms. Radiologically, these can present as consolidation, well-defined mass or nodules. So, PPL can easily be confused radiologically with primary lung carcinoma or metastases when presenting as multiple masses or/and nodules but they have different treatment and prognosis. The main diagnostic criterion for PLL is the absence of extra-pulmonary involvement. Therefore, in patients with biopsy-proven lymphoma of the lung, PLL is diagnosed if extra-pulmonary involvement is ruled out. B-cell primary pulmonary NHL are subdivided into low-grade B-cell PPLs (58–87 %), high-grade B-cell PPLs (11–19 %). The high-grade B-cell PPLs spread rapidly into mediastinal and extra-thoracic locations. This may lead to underestimation of true incidence.

Primary Pulmonary MALT Lymphoma (W.H.O. Classification ICD-O Code 9699/3)

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 mucosa-associated lymphoid tissue (MALT) of the bronchus, which is 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 are also in the bowel, salivary glands, larynx, and thyroid gland [22]. Unlike the model of gastric MALT lymphoma and *Heilcobacter pylori*, no triggering of antigens has been identified in the primary

pulmonary MALT lymphoma. Among the non-gastrointestinal MALT lymphomas the pulmonary lymphomas are the most frequent, (up-to 19 % among MALT lymphomas) [23, 24].

Pulmonary MALT-lymphomas seem to arise on pre-existing inflammatory accumulations of organised lymphoid tissue (lymphoid follicles of the bronchus-associated lymphoid tissue – BALT). BALT is inconspicuous in adults, but the tissue undergoes hyperplasia in patients with chronic immune-mediated diseases such as chronic infections, connective tissue diseases, rheumatoid arthritis, and Sjogren's syndrome. The cause of these inflammatory processes is 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 [24]. Accordingly, the occurrence of intraclonal sequence variations (ongoing mutations) is a common finding in both gastric and pulmonary lymphomas, indicating the role of antigen stimulations in their pathogenesis [24, 25]. In a proportion of pulmonary lymphomas correlations have been clearly established with conditions where the immune system is abnormally stimulated or deregulated, such as in autoimmune diseases (Sjogren's syndrome, Hashimoto thyroiditis, systemic lupus erythematodes -SLE, rheumatoid arthritis), or immunodeficiency (primary or acquired). On the other hand, data regarding infections are scanty, and include occasional reports of pulmonary lymphoma with concomitant infectious diseases (*Mycobacterium avium* complex, *Hepatitis-C virus*, *Helicobacter pylori*). Very rarely an association between yellow nail syndrome and MALT lymphoma in the lung has been reported.

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 by accident. 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 [24]. This indolent behaviour can explain why many cases of pulmonary MALT-lymphoma have been previously defined as "pseudolymphoma" [24–27]. 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 immunoelectrophoresis is found.

Radiologic feature of MALT lymphoma are solitary, well-delineated soft-tissue masses with air bronchogram. Although hilar and mediastinal lymphadenopathy is not a prominent radiologic finding, nodal involvement is documented at pathologic analysis in about the 30 % of cases. HRCT findings include: areas of aveolar consolidation more frequently centred on dilated bronchi, ground glass attenuation, the presence of the "halo sign", peribronchovascular nodules, "tree in bud pattern", peribronchovascular thickening and septal lines [28]. The lesions are multiple in more then 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 endotracheobronchial MALT lymphoma with polypoid features have been reported causing also unilateral lung hypertransparency. MALT lymphomas have generally been reported not to show increased fluorine 18-fluorodeoxyglucose (18-FDG) accumulation on positron emission tomography (PET). The outcome of MALT-type primary pulmonary lymphoma is generally favorable. More than 80 % of the cases have a 5-year survival rate, and the median survival rate has been more than 10 years. The overall survival is better than other types of non-Hodgkin's lymphoma [16–21]. Clinical features associated with poor prognosis in a series study of primary pulmonary lymphoma included patients over 60 years of age, elevated serum lactate dehydrogenase and elevated serum beta2 microglobuin levels.

Cytogenetic Features and Molecular Pathogenesis

As in other extranodal-MALT lymphomas, an heterogeneous pattern of cytogenetic abnormalities has been demonstrated in pulmonary lymphomas, including aneuploidy (observed in nearly 40 % of cases, with trisomy 3 and 18 being the most common), and specific chromosomal translocations. Translocation t(11;18)(q21;q21) which characterizes about one third of extranodal marginal MALT lymphomas is the most frequent chromosome translocation occurring in pulmonary MALT lymphomas (38.3–41 % in different series). This translocation involves the API2 and MALT1 genes, and can be then directly correlated to the pathogenesis of this lymphoma [29]. Accordingly, API2 is a member of the IAP (inhibitor of apoptosis) gene family, whereas MALT1, a paracaspase of unknown functions, is able to interact with bcl-10 inducing NF-kbeta (nuclear factor K beta) activation. The abnormal fusion of MALT1 with API2 produces chimeric transcripts involved in inhibition of apoptosis, thus contributing to lymphoma development. 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 characterised by the absence of any underlying autoimmune disease and lack of plasmacytic differentiation.

Information regarding the occurrence and frequency of other genetic abnormality involved in the pathogenesis of MALT lymphomas such as t(1;14)(p22;q32) are scanty.

Histology Characteristics

At histological analysis the pulmonary structure is effaced by abnormal lymphocyte infiltration, predominantly localised along bronchovascular bundles, interlobular septa and visceral pleura, in a lymphangitic pattern [30]. As MALT lymphomas arising at other sites, pulmonary MALT-lymphoma is formed by the accumulation of clonal lymphoid cells characterised by the morphological and biological features of marginal-zone B-cells. Marginal-zone cells, that are particularly abundant in the spleen, are post-germinal centre 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 cells), characterised 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 characterised by accumulation of lymphoid follicles, and in particular the spectrum of follicular hyperplasia, follicular bronchiolitis, and lymphocytic interstitial pneumonia, as well as, more rarely, hypersensitivity pneumonitis, inflammatory pseudotumor, intraparenchymal thymoma, and Castleman's 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 [31].

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 etio-pathogenesis presenting as isolated nodules or diffuse) can in fact be included in the clinicopathologic spectrum of MALT lymphomas, together with localised pulmonary amyloidosis (another lesion that has been described in association with pulmonary marginal lymphoma).

Clinical Vignette

A 75-year-old man with a history of progressive impairment of general condition, intermittent fever and weight loss was admitted. The peripheral blood picture was unremarkable. Right-sided pneumonia and both-sided pleural effusions revealed by X-ray examinations. Chest CT showed areas of aveolar consolidation with air bronchogram, ground glass attenuation, the presence of the "halo sign" and peribronchovascular nodules (Fig. 31.4a–c). The radiological picture appeared to be definitely deteriorated to a control of chest CT after 40 days and after antibiotic treatment with macrolides. The clinical conditions was deteriorated too. Transbronchial lung biopsies via rigid bronchoscopy were performed but the pathologic examination was inconclusive. Therefore transparietal fine needle aspiration/biopsy samples obtained under CT guide were performed and the pathologic examination noted an histologic pattern compatible with non specific interstitial pneumonia (NSIP). However, this was not harmonized with the clinical and radiological feature (even considering the significant increase of right pleural effusion). Furthermore at this time the laboratory tests revealed anemia (Hb 6.5 gr/dl).

We suspected some lymphoproliferative process and medical thoracoscopic lung biopsy was performed that revealed primary pulmonary MALT lymphoma by immunohistochemical analysis of pleural tissue specimens (Fig. 31.5a–c). Bone marrow examination was negative.

Pulmonary Plasmacytoma (W.H.O. Classification ICD-O Code 9731/3)

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 [32, 33]. It is an extremely rare tumour, 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 is difficult and is usually based on the excised tissue

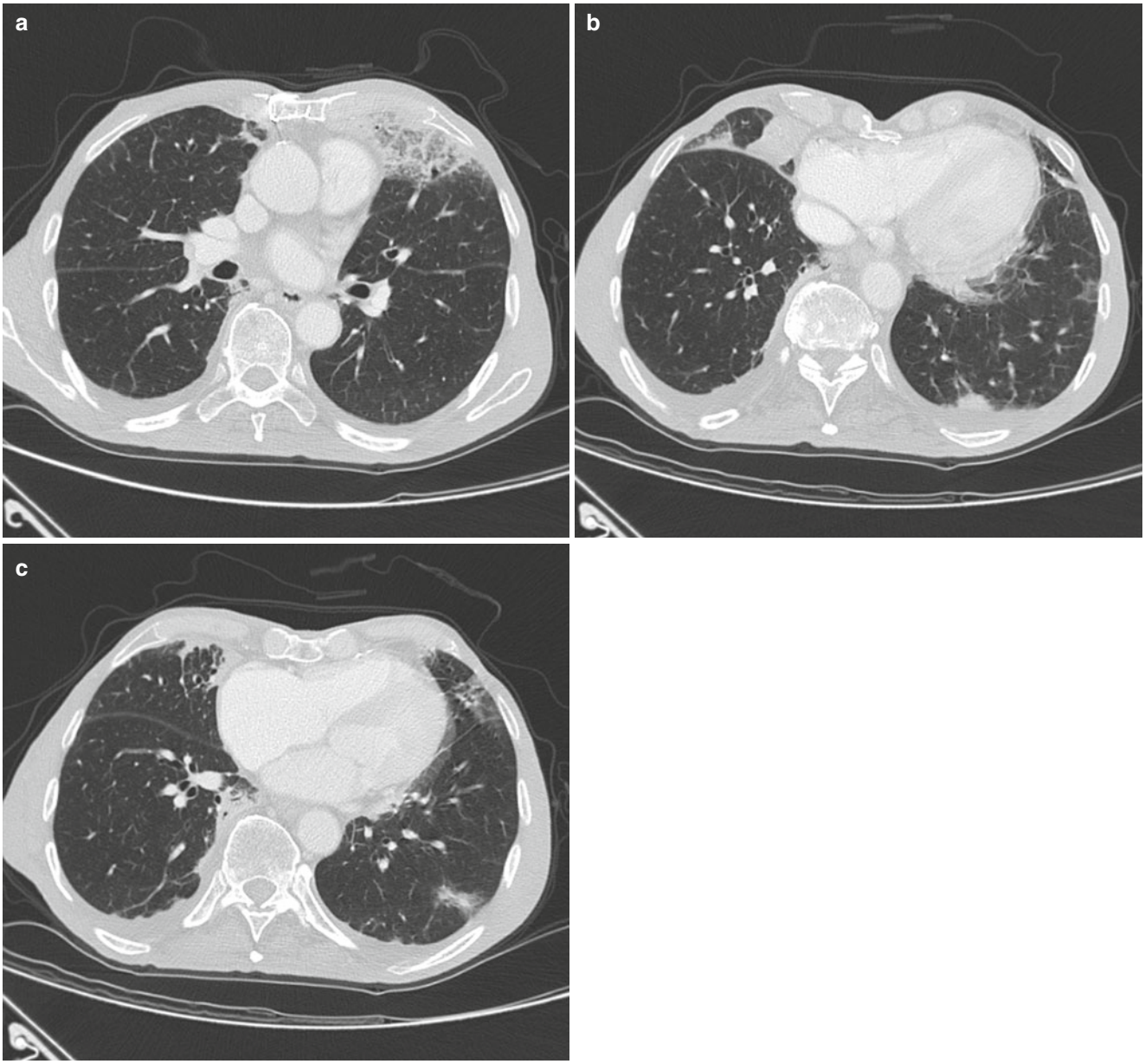

Fig. 31.4 CT scan shows bilateral consolidations, particularly in the middle lobe (**b**) and in the posterior segment of left lower lobe (**b**). Moderate ground glass attenuation with interlobular septal thickening is present in the lingula and in the middle lobe. Moderate bilateral pleural effusion

The less differentiated plasmablastic pulmonary plasmacytoma occurs mainly in patients with advanced HIV infection. Phenotypically similar to mature plasma-cells, the malignant cells appear most like plasmablasts. Prognosis in HIV + patients is poor (5.5 months) even if recent small reports suggest it may have improved after HAART advent. The relationship between plasma cell myeloma, solitary plasmacytoma of bone, and extraosseous plasmacytoma is not well understood. For some authors these 3 entities represent different aspects of the same disease spectrum. 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, dyspnoea and haemoptysis. Laboratory features include paraproteinemia and urinary Bence Jones. When involving lung 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 [34]. Little is known about

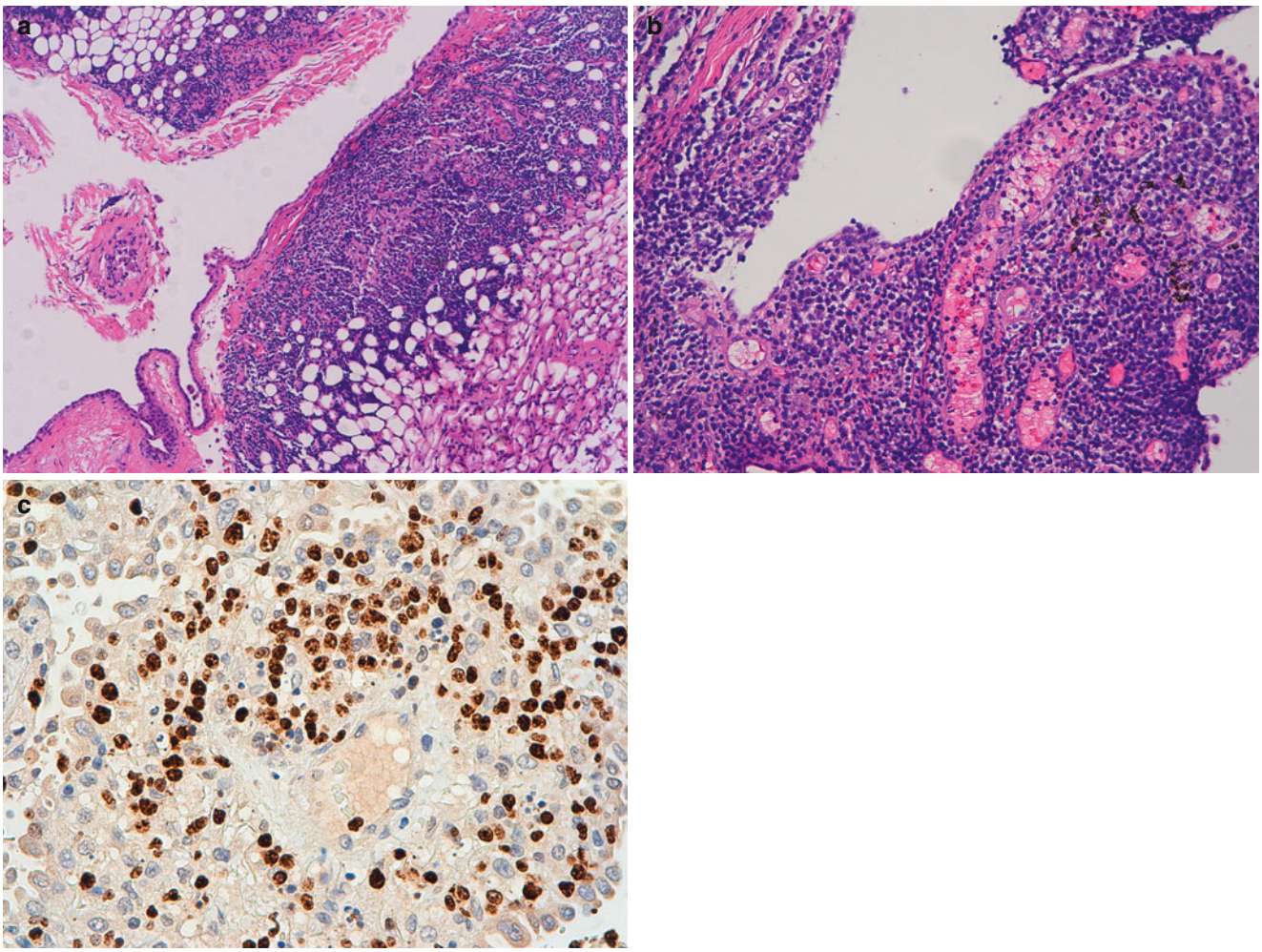

Fig. 31.5 Medical thoracoscopic lung biopsy; (**a**) In this low magnification view, the neoplastic cells infiltrate extensively the parietal pleura; (**b**) High magnification view of the pleural neoplastic infiltrate composed of small to medium-sized b lymphocytes with relatively abundant, pale cytoplasm; occasional plasma cells are present. (**c**) Malt lymphoma with t (11;18) (q21;q21); API2/MALT1 FISH study using a orange probe against MALT1 and *green probe* against API2. The normal genes appear as isolated *orange* or *green* signals, while evidence of the fusion gene (insert) appears as a *yellow* signal

endoscopic findings, but as occurred in our third patient, infiltration of the mucosa has been observed, along with polypoid tumors, all lesions which are comparable to those seen in bronchogenic carcinoma [35].

Follicular Lymphoma (W.H.O. Classification ICD-O Code 9690/3)

Follicular lymphoma is generally an indolent B-cell lymphoproliferative disorder of transformed follicular center B cells. Follicular lymphoma is characterized by diffuse lymphoadenopathy, bone marrow involvement, splenomegaly, and less commonly other extranodal sites of involvement such as gastrointestinal tract, lung, skin and other sites [36].

It affects adults (median age 59 years) and it is more frequent in females (male/female ratio 1/1.7). In general, cytopenias can occur but constitutional symptoms of fever, nightsweats, 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 of preferably biopsy. Immunohistochemical staining is positive in virtually all cases for cell surface CD20, CD10, nuclear for Bcl6 and monoclonal immunoglobulin, as well as membrane expression of bcl-2 protein. The overwhelming majority of cases have 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 <12 g/dL, 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.

The most patients are treated with chemotherapy plus rituximab (anti-CD20), which has improved response rates [37].

High-Grade Primary Large Pulmonary B Cell Lymphomas

High-grade primary large pulmonary B cell lymphomas represent a minority of cases of primary pulmonary lymphoma (11–19 %). Often occur in patients with underlying immunological disorders such as immunosuppression in solid organ transplantation, HIV infection and Sjogren syndrome [38]. Patients are usually symptomatic with respiratory symptoms (cough, dyspnoea, haemophtysis), fever and weight loss.

Common radiological and CT findings include single pulmonary mass, not infrequently escavated, and atelectasis; pleural effusion may be present. In HIV patients or in other immunosuppressed hosts, multiple excavated opacities are more frequently found.

Median survival time is 8–10 years, but relapse and progression occur early and survival is dramatically poorer in patients with underlying immunologic disorders such as AIDS and transplantation.

Intravascular Large B-Cell Lymphoma (W.H.O. Classification ICD-O Code 9680/3)

Clinical Vignette

A 61-year-old woman with a short history of progressive impairment of general condition, intermittent fever and worsening dyspnea was admitted. She had an unremarkable medical history until some days ago when she was referred for impairment of general condition, fever, sick, diarrhea and worsening dyspnea. Clinical and radiological examination showed no evidence of pneumonia or bronchiolitis. The peripheral blood picture was unremarkable except for the serum lactate dehydrogenase level that was elevated at 3401 U/L (normal range 120–240 U/l) and platelet count that was 69 g/L. The patient presented acute respiratory failure, with moderate hypoxemia of PaO_2 56 mmHg, $PaCO_2$ 21 mmHg and PH 7.36 while breathing room air O_2. 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. 31.6a, b). The ventilation/perfusion lung scan indicated a low probability of pulmonary embolism. Antinuclear antibodies was mild positive while the rheumatoid factors, and anti-neutrophil cytoplasmic antibodies were negative. Based on this finding and the suspicion of an undifferentiated connective tissue disease was started on treatment with methylprednisolone i.v. at a dose of 250 mg daily. However 3 days after, the patient was transferred to the intensive care unit because of progressive respiratory insufficiency, necessating ventilation support. Additionally, pancytopenia was aggravated (29 g/L) but the most striking laboratory feature was massive elevations of LDH (4398 U/l); indicating hyperproliferation. Cardiac ultrasonography excluded an acute right heart insufficiency but showed a minimal pericardial effusion. After 2 days, while intubated, the patient died of rapidly progressive respiratory failure. Autopsy findings were consistent with intravascular lymphoma involving the lung (Fig. 31.7a–b).

Intravascular Large B-Cell Lymphoma

Intravascular large B-cell lymphoma is a rare subtype of B-cell lymphoma with an estimated frequency of <1 % of all lymphomas and characterized by an intravascular proliferation of clonal lymphocytes with little to no parenchymal involvement and usually without involvement of lymphoid tissues and occasionally peripheral blood. A variant may be primary large cell lymphoma of the splenic sinuses and single cases of aggressive lymphoma of T-cell with an angiotropic growth pattern have also been reported [39–41].

Proliferation of lymphoma 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. Therefore, the diagnosis is often difficult [42, 43].

Intravascular lymphoma usually shows rapid progression and short survival, with at best transient remissions. The very poor prognosis in these patients reflects in part frequent delays in diagnosis and initiation of therapy due to their extraordinary presentation.

A case of pulmonary arterial hypertension and a case of respiratory insufficiency with air trapping have been reported. LDH, soluble interleukin 2 receptor (sIL-2R) and ESR are usually elevated. Pulmonary function tests show a markedly decreased diffusing capacity.

Chest X-ray may be normal or show reticulonodular infiltrates or pleural effusion. CT findings may include bilateral reticular shadow, reticulonodular shadow, ground glass opacity, wedge-shaped subpleural opacities and pleural effusion [39–43]. F-fluorodeoxyglucose positron emission tomography (18-FDG-PET) shows increased FDG uptake. A ventilation/perfusion (V/Q) scan may document a mismatched segmental defect identical to that observed in pulmonary thromboembolism. An *ante mortem* diagnosis is difficult. Transbronchial biopsies can assist with the diagnosis, as can

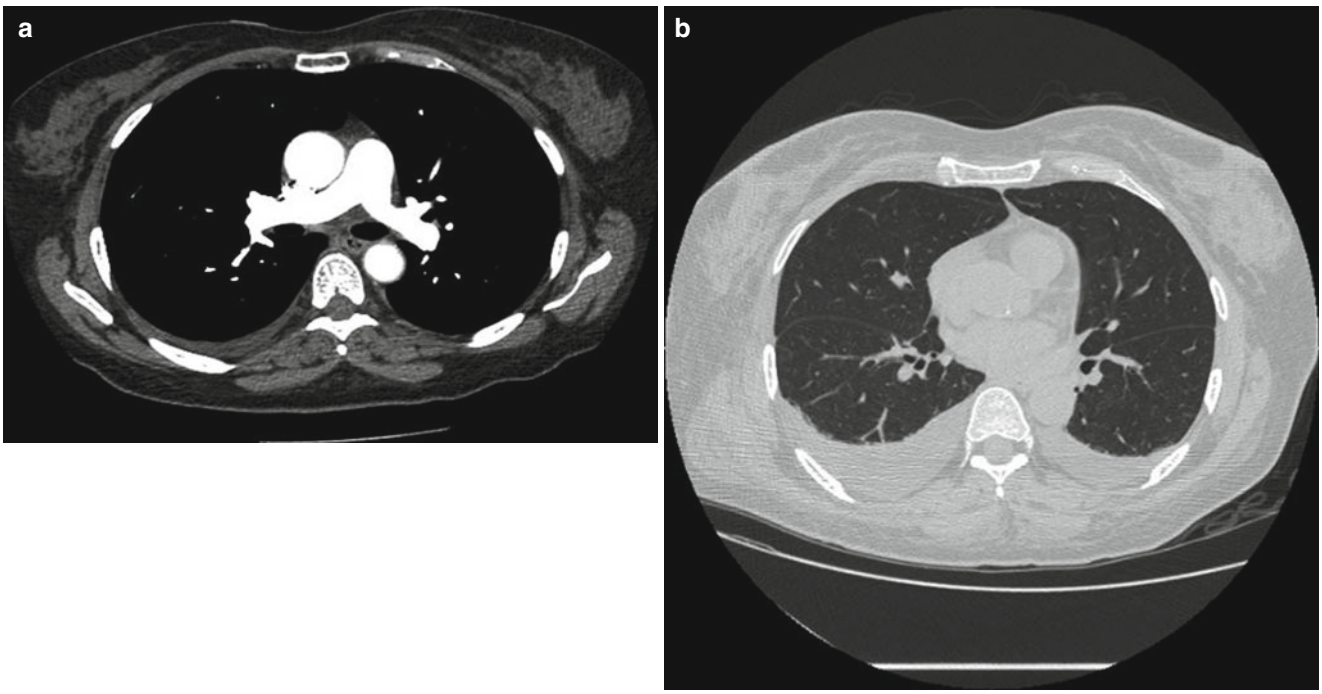

Fig. 31.6 (**a**–**b**) A contrast enhanced CT of the chest ruled out any proximal or sub-segmental pulmonary embolism but shown a mild bilateral pleural effusion and no parenchymal involvement

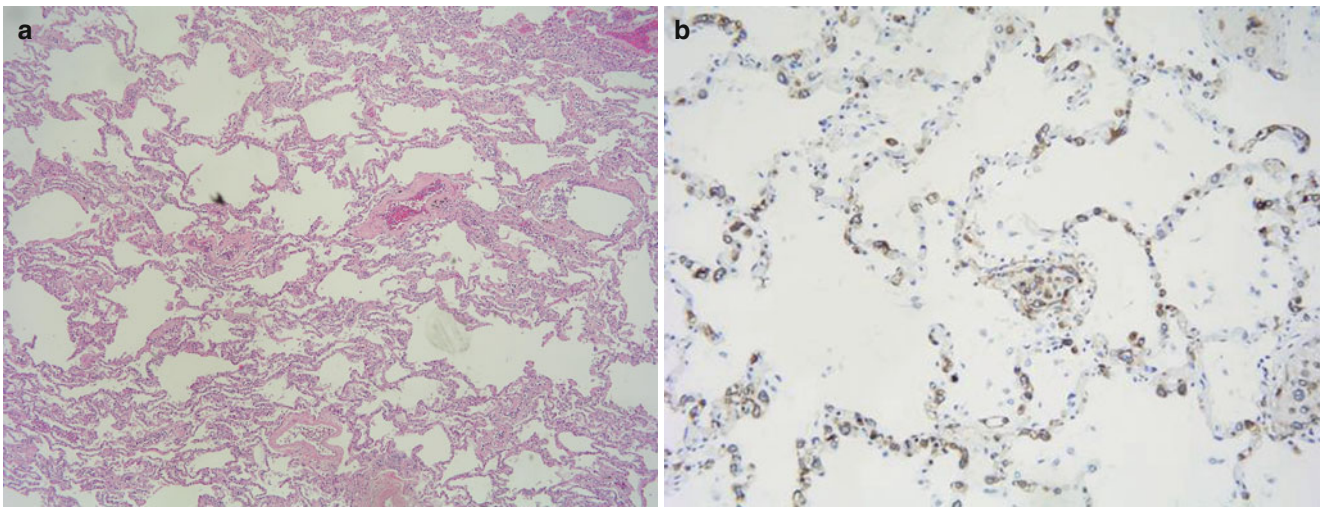

Fig. 31.7 Autopsy findings; (**a**) The neoplastic lymphoid cells are mainly lodged in the lumina of vessels in the lung tissue. The tumor cells are large with prominent nucleoli. (**b**) The tumor cells are highlighted by staining with CD20

cytological analysis of pulmonary capillary blood cells. Despite intense efforts, the definitive histopathological diagnosis of aggressive B-cell lymphoma is often not established before the patient died. Only autopsy revealed the presence of an intravascular large B-cell lymphoma, which obviously progressed rapidly in the final days. Splenomegaly, pancytopenia, erythroblastosis and massive elevation of LDH levels urgently suggested the presence of a hematological neoplasia, in particular a myeloproliferative syndrome or aggressive lymphoma. In conclusion,a highly elevated LDH and pancytopenia without lymphadenopathy, associated with a leukoerythroblastic picture in peripheral blood should prompt the clinician to consider intravascular lymphoma as a possible differential diagnosis. The initiation of an intensive diagnostic work-up in that direction is of paramount importance since a potentially curative therapeutic option is available, but only at an early stage of the disease (3943). Prognosis is usually very poor in spite of combination chemotherapy.

Histology Characteristic

Histology shows subtle changes and is characterized by small pulmonary vessels and dilated capillaries showing intraluminal infiltration of medium sized cells with ovoid hypercromatic nuclei. The neoplastic cells are immunoreactive for leukocyte common antigen (LCA) and B-cell markers. Compared with non-neoplastic leukocytes, large malignant lymphocytes appear either negative or only weakly positive for the leukocyte surface glycoprotein, CD18 that is the beta chain of the CDIIa/CD18 complex (lymphocyte-function associated antigen-I, LFA-I), which mediates cell-to-cell adhesion of lymphocytes. Further, the malignant lymphoid cells stain positively with Hermes-3 antibody, which recognizes a common structure of CD44 class of molecules involved in lymphocyte homing. Molecular investigations may confirm a monoclonal rearrangement of the heavy- chain gene.

Lymphomatoid Granulomatosis (LYG, W.H.O. Classification ICD-O Code 9766/1)

Lymphomatoid granulomatosis is an extranodal angiocentric and angiodestructive lymphoproliferative disorder characterized by a polymorphic lymphoid infiltrate, an angiitis, and granulo-matosis [44]. Data indicate that LYG is an Epstein-Barr virus (EBV) positive B-cell proliferation associated with an exuberant T-cell reaction [45]. Although it may affect virtually any organ, it is most frequently characterized by pulmonary, skin and central nervous system involvement. This condition usually affect adults (average age 50) with a predilection for male (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 [46]. In LYG, lung is the most frequently involved site [47], while the upper respiratory tract is less commonly involved, ulceration of the upper airways having been described in 10–30 % of cases. Other sites of involvement are brain, kidney, liver, skin, soft tissues, bladder and gastrointestinal tract.

Few subjects are asymptomatic. Nearly 90 % of patients report chronic respiratory symptoms, mainly cough, chest pain and dyspnoea accompanied by B-symptoms such as fever, weight loss and sweating. Haemoptysis, or acute respiratory distress syndrome rarely occur. Laboratory findings are characterized by increased ESR and, in a minority of cases by lymphopenia, leukocytopenia and low CD4+ lymphocyte count.

Lung nodules are the most common feature in Chest X ray films occurring in perhaps 80 % of cases, and cavitation may be noted in a 20 % of cases. Pulmonary nodules are the most common findings also on CT images [48]. The margins of the nodules are usually irregular, but well-defined and distributed along the bronchovascular bundles or interlobular septa [47, 48]. Recently it has been reported a case of lymphomatoid granulomatosis with an atypical CT finding of crescent sign for LG. Typically, LG patients with lung involvement can present with pulmonary infiltration and may later develop a reversed halo sign, a focal round area of ground-glass attenuation and surrounding airspace consolidation of crescent shape. Although the reversed halo sign is relatively specific to a diagnosis of cryptogenic organising pneumonia, there have been reported cases of a reversed halo sign in patients with LG, sarcoidosis, pulmonary paracoccidioidomycosis and other pulmonary fungal infections as well [49].

This distribution can be explained by the angiocentric distribution of lymphomatoid granulomatosis. Small thin-walled cystic lesions and as well as masses growing through the lumen of the pulmonary artery with vascular occlusion may also be present. Magnetic resonance imaging (MRI) or contrast-enhanced CT in patients with lymphomatoid granulomatosis who have hilar masses may help to determine the presence and extent of arterial narrowing or occlusion. In about 30 % of patients pleural effusion is present at the beginning. Hilar adenopathies are found in less than 25 % of cases. Uncommon radiologic features reported in literature are: single nodules, alveolar opacities and reticolonodular diffuse lesions. Differential diagnosis in patients with LYG is a real challenge: Wegener's granulomatosis, other necrotizing vasculitides, necrotising nodular sarcoidosis, infections, bronchogenic carcinoma and metastatic tumours [47], organizing pneumonia, and very rarely acute lung injury are in the top list.

The clinical course is highly variable [50]. 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 [51]. One-third of patients with grade 1 lesions progress to malignant lymphoma, whereas two-thirds of patients with grade 2 lesions develop lymphoma. Patients affected by the aggressive form of disease are leading to death in 2 years, in spite polychemotherapy. Death is often caused by a progressive pulmonary involvement. However high-dose therapy followed by autologous stem cell transplantation (ASCT) and alloSCT are effective therapeutic options and should be considered in all patients with refractory and multiply relapsed LG [52] but an other study has shown a long-term remission after multiple relapses in an elderly patient with lymphomatoid granulomatosis after rituximab and high-dose cytarabine chemotherapy without stem-cell transplantation [53].

Histology Characteristic

Lymphomatoid granulomatosis (*LYG*). The term LYG includes a group of related lesions characterised by the

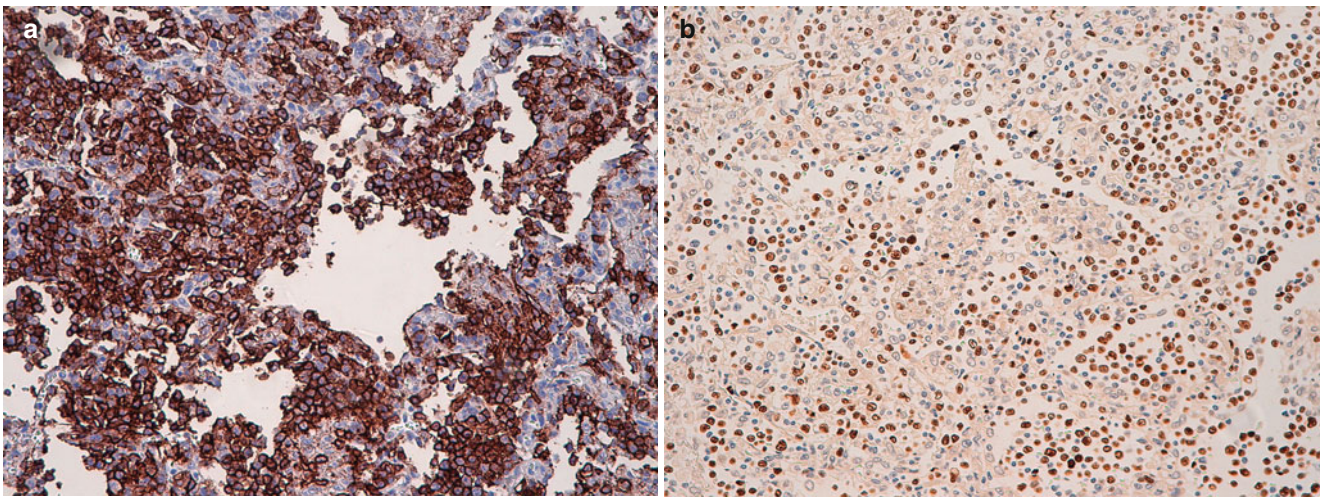

Fig. 31.8 (**a**) Lymphomatoid granulomatosis: the lymphomatous cells have B: CD20+ (10× IIC). (**b**) Lymphomatoid granu-lomatosis: positive signals of EBV in the nucleus of lymphomatous cells by in situ hybridization with EBER (Epstein Barr virus encoded RNAs) probe (10× IIC)

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 expression of B-cell related antigens CD20 and CD79a, and EBV markers such as latent membrane protein-1 (LMP-1) and EBV-encoded RNA (EBER) [50]. The lymphoid infiltrate often surrounds muscular pulmonary arteries and veins and typically invades the walls of these vessels. Necrosis is a frequent, although not universal, feature of the disease (photos 9abc). 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 characterised by varying proliferation index and prognostic differences. 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 with double nuclei 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. Similarities therefore exist between PTLD and LYG: grade 1 cases may be EBV driven polyclonal lymphoproliferations, and grade 2 cases may be similar to polymorphous, monoclonal PTLD, in which some degree of immunodeficiency allows proliferation of clonal EBV + cells; grade 3 forms are true monomorphous diffuse large B-cell lymphomas. 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 need to be distinguished, histologically, from other diseases characterised by polymorphous lymphoid infiltration (angioimmunoblastic lymphoadenopathy, infection due to *Epstein Barr* virus, acute and fibrinous organizing pneumonia, inflammatory sarcomatoid carcinoma, other malignant lymphomas in particular enteropathy-associated T cell lymphoma and acute T cell lymphoblastic leukemia), and/or by zonal coagulative necrosis and prominent angioinvasion [including extranodal NK/T (nasal-type) T-cell lymphoma, and Wegener's granulomatosis] [50] (Fig. 31.8a–b).

T/NK-Cell Primary Pulmonary Lymphomas

Very few cases of T-cell PPL, the majority diagnosed by open lung biopsy, have been described in medical literature. T-PPL comprises a group of rare, aggressive cancers that develop from T-cells that are at different stages of maturity. The World Health Organization (WHO) has divided the various types of PPL into two main categories: (1) precursor T-cell neoplasms, which include T-lymphoblastic lymphoma/leukemia; and (2) peripheral T-cell neoplasms, which are subcategorized as predominantly leukemic disease, predominantly disseminated disease, predominantly extranodal disease and predominantly nodal disease. Patients with T-PPL are usually adults with generalized disease; the lymph nodes, liver and spleen may be involved [54]. Most of the cases present with cough and dyspnea. The most common radiologic finding of PPL is generalized lymphadenopathy [55] however it has been reported cases of bilateral

pulmonary nodules, diagnosed with T-cell PPL. T-PPL should be included in the differential diagnosis of patients with fever and bilateral pulmonary nodules. In patients with disseminated conditions, the imaging features are not distinguishable from those of the other subtypes of lymphoma in the disseminated state.

Different types of extranodal T-cell lymphomas can occur primary in the lungs: nasal-type T/NK lymphoma, anaplastic large T cell lymphoma, mycosis fungoides, peripheral T-cell lymphoma unspecified [56]. Due to their rarity only anectodal descriptions of their features are available. Recent reports have shown T-cell lymphomas occurring at a grater rate in HIV infected individuals than in HIV- subjects [50].

Nasal-Type T/NK Lymphomas (W.H.O. Classification ICD-O Code 9719/3)

Nasal-type T/NK lymphomas in the lung present clinico-radiologial features similar to LYG. CD4+ lymphopenia and systemic symptoms such as fever, malaise, weight loss, and hemophagocytic syndrome are not infrequent. Lung involvement may show nodules or excavated masses [57]. Pleural effusion may also be present.

Histology Characteristics

Nasal-type T/NK lymphomas when occurring in the lung can present many similarities with LYG, including angioinvasion, expression of markers of EBV infection, necrosis, immune disturbances and a rich T-cell infiltrate exhibiting cytotoxic immunophenotype, as defined by the expression of CD8, TIA-1, granzyme-B, and perforin. The occurrence of EBV marker expression is heterogenous in pulmonary T-cell lymphomas (Fig. 31.9a–f).

Anaplastic large cell lymphoma, T-cell type (ALCL, W.H.O. ICD-O code 9714/3), was previously recognised as Ki-1 lymphoma for the strong expression of the activation antigen CD30/Ki-1.

Anaplastic large T cell lymphoma (*W.H.O. classification ICD-O code 9714/3*) has rarely been described as primary pulmonary presentation; masses or single nodules are the features observed at CT, The patient present with B symptoms.

Mycosis fungoides (*W.H.O. classification ICD-O code 9700/3*) in its rare granulomatous variant may involve primary the lungs. Clinically 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 [58]. Due to its rarity and lack of clinico-radiological specificity the diagnosis is always difficult and require accurate histopatological analysis [59]

Primary Pulmonary Hodgkin's Disease (PHD)

PHD is a rare entity and has to be distinguished from the more common intrathoracic nodal Hodgkin's disease secondarily involving the lung [60, 61]. Due to its rarity epidemiological data of primary pulmonary PHD are scarce. In a review of 60 cases recorded in the world literature PHD is affecting women more frequently than men and that it shows bimodal age distribution (<35 yrs and >60 yrs) and there is no significant correlation with cigarettes smoke [62]. 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 [63]. Compared to non-Hodgkin's lymphoma, Hodgkin's disease more often presents as a nodular lesion. Rarely, it manifests as a diffuse infiltrate along the lymphatic routes. Sometimes an interesting pattern may be noted at the periphery of nodular masses: pneumonic consolidation of architecturally intact air spaces by fibrin, fibroblasts in a mucopolysaccharide-rich matrix, and a cellular infiltrate of Hodgkin's disease. Since the presentation of this disease is non-specific, and as noninvasive tests are rarely revealing, diagnosis often requires open thoracotomy and lung biopsy.

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 [50]. Hodgkin's lymphoma is linked to HIV infection with a relative risk of 11.5 %. In HIV + patients often shows two unfavourable subtypes: lymphocyte-depletion and mixed cellularity; in non-immunocompromised hosts the nodular sclerosis variant is usual. The differential diagnosis includes tuberculous and fungal granulomas, metastatic carcinomas and Non-Hodgkin's lymphoma particularly T-cell lymphomas, polyangiits and granulomatosis, Langerhans histiocytosis. If extensive necrosis and granulomas are seen, the presence of Reed-Sternberg cells help to exclude infectious granulomas and polyangiits and granulomatosis. Large number of eosinophils may cause Langerhans histiocytosis to be considered, but Langerhans cells lack the malignant characteristics of Reed-Sternberg cells. Undifferentiated carcinomas may show the presence of Reed-Sternberg like cells, but neutrophils are frequently seen and eosinophils are seldom present. In difficult cases immunohistochemistry resolves the diagnostic problem. Exclusion of other types of lymphoma may be impossible on routine histology. Some forms of T-cell lymphomas may simulate Hodgkin's disease by showing extreme degree of cellular pleomorphism and a background of reactive inflammatory cells. Immunohistochemistry is required. Treated patients relapse within 2 years and clinical

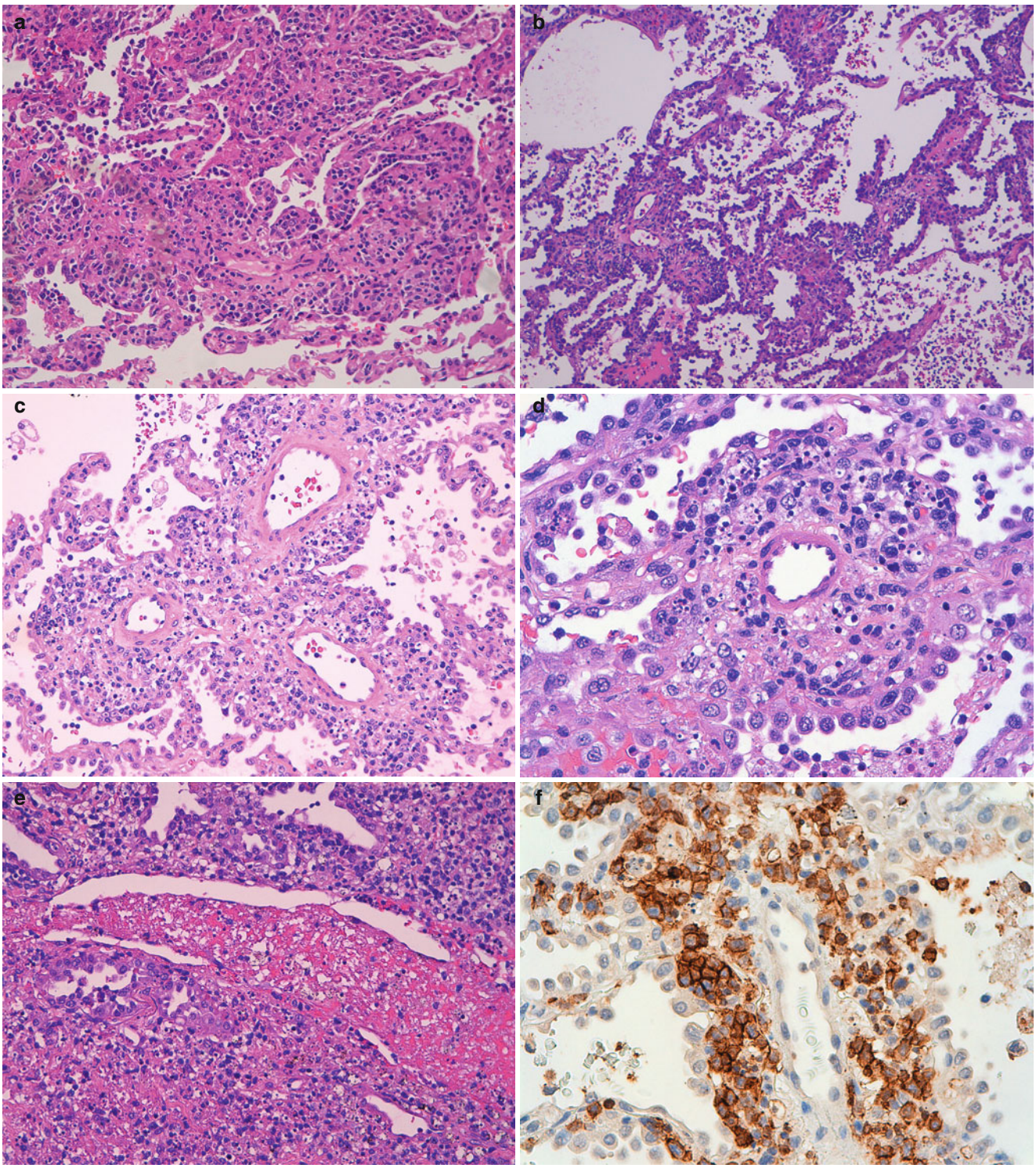

Fig. 31.9 (**a**) Extranodal NK/T lymphoma, nasal type: the lymphomatous infiltrate shows interstitial perivascular infiltration of small, medium-sized cells with irregular nuclei (2× EE); (**b**) Extranodal NK/T lymphoma, nasal type: the lymphomatous infiltrate shows interstitial perivascular infiltration of small, mdium-sized cells with irregular nuclei (4× EE); (**c**) Extranodal NK/T lymphoma, nasal type: the lymphomatous infiltrate shows interstitial perivascular infiltration of small, mdium-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 infitration 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)

relapse result in a high mortality. Patients older than 60 years with B symptoms, multiple and bilateral lesions and HIV infection have even a worse prognosis. Furthermore, patients treated for Hodgkin's lymphoma have a higher risk of developing second lung cancer (SLC) compared with the general population [63].

Histology Characteristics

Neoplastic nodules are formed by an heterogeneous cell population, including many inflammatory cells (macrophages, T lymphocytes, plasma cells, granulocytes) and isolated atypical cells characterised by the cytological features of Reed-Sternberg/Hodgkin's cells of the classic-type HL (as defined in the W.H.O. classification, ICD-0 code 9650/3). Immunophenotypic analysis can be highly useful in characterising Reed-Sternberg/Hodgkin's cells. Studies have precisely defined the molecular profile of these cells, which are in fact B-cells with defects in the mechanisms of immunoglobulin production, and are recognised by the absent (or very low) expression of B-cell related markers (Bob-1, Oct-2, CD79a), as well as by the strong expression of activation markers (CD30, CD15, MDC, fascin) [64, 65]. Various modifications can be observed in the parenchyma adjacent to the neoplastic nodules of Hodgkin's lymphoma, including focal organising pneumonia, endoalveolar accumulations of foamy macrophages and interstitial lymphoid infiltration.

Post-Transplantation Lymphoproliferative Disorders (PTLD)

Post-transplantation lymphoproliferative disorders (**PTLD**) develop in organ or bone-marrow transplant recipients and range from benign lymphoid hyperplasia to frank malignant lymphoma which is a potentially lifethreatening complication that occurs in approximately 1.7–3.5 % of solid-organ transplantation recipients [66].

The clinco-pathological features comprehend "Benign plasmacytic hyperplasia and infectious-mononucleosis-like PTLD" which arise in oropharinx or lymphnodes and are polyclonal; "polymorphic lymphoproliferative disorder" that may be nodal or extra-nodal 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. Incidence vary 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 %) but those who receive HLA-mismatched or T-cell depleted bone marrow and those who receive immunosuppressive therapy for graft versus host disease (GVHD) are at the highest risk for development of lymphoma (up to 20 %). The majority of PTLD are associated with *Epstein Barr virus* infection.

The median time interval from transplantation to diagnosis is about 8 months (with a wide range of 1–97 months, being it shorter in patients receiving heart, lung, or stem cells/bone marrow transplants). High values of ESR and C-reactive protein (CRP) is common, whereas plasmacytic hyperplasia and polymorphic lymphoproliferative disorder are usually asymptomatic and generally regress spontaneously following withdrawal of immunosuppression. The majority of patients have a negative serology for *Epstein Barr virus* and *cytomegalovirus* before transplantation. An other key risk factor is the HLA matching.

Typical radiological findings are single or multiple nodules with hilar or mediastinal adenopathy, interlobular septal thickening, air space consolidation. Nodules with peripheral ground glass attenuation (halo sign) may imitate invasive mycoses. They can also have involvement of serous surfaces and can develop pleural effusions from which tumor cells can be recovered.

Histology Characteristics

In plasmacytic hyperplasia and infectious-mononucleosis-like lesions there is a mixture of polyclonal B cells, plasma cells, and T cells. There is evidence of multiple EBV infectious events and no evidence of oncogene or tumor-suppressor gene alterations. Pleomorphic PTLD are composed of immunoblasts, plasma cells, and intermediate-sized lymphoid cells that form destructive masses in the lung parenchyma. There may be areas of necrosis and numerous mitoses may be present. Molecular genetic studies virtually always show clonal rearrangement of immunoglobulin genes and/or EBV genomes, but cytogenetic analysis and studies of oncogenes such as *myc*, *ras*, and *TP53* typically show no mutation. These lesions display variable clinical behaviour, their progression correlating with bcl-6 gene mutations. Monomorphic PTLD consist of areas of necrosis surrounded by a dense monomorphic lymphoid infiltrate (angioinvasive and destructive infiltrate); the cells appear to be transformed (large, blastic cells with prominent nucleoli and basophilic cytoplasm). A plasmoblastic differentiation may be prominent. They show clonal Ig gene rearrangement or, less frequently, clonal T-cell receptor gene rearrangement. In cases of B cell type EBV genomes, in clonal episomal form, are present in the majority of cases. About a quarter of monomorphic T-PTLDs have clonal episomal EBV genomes. Alterations of one or more oncogenes or tumor-suppressor genes are present

Diagnosis and Staging

Due to their rarity and heterogeneity the diagnosis of these lymphomas can be occasionally problematic if solely based

on histological analysis, so that the use of more sensitive and precise techniques is recommended including immunophenotypic analysis by immunohistochemistry and/or flow cytometry, and molecular biology.

Different surgical procedures may be used to obtain diagnostic tissue. Endoscopic bronchial or trans-bronchial biopsy is the most frequently used technique. When the lesion appears in the central airways big biopsy obtained by rigid bronchoscope are generally sufficient for a precise diagnosis [67]. Open-lung biopsy or video-assisted thoracoscopic surgery can be chosen if tissue from endoscopy biopsy is not sufficient. Bronchoalveolar lavage does not allow making a complete morphologic analysis for an accurate diagnosis of lymphoma, but can be highly improved when molecular and immunophenotypic studies are available [68, 69].

The diagnostic yield of **transbronchial biopsy** is higher when it targets visible radiographic abnormalities [70]. CT imaging play an important role in directing the bronchoscopist 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 ultrasonography** (**EBUS**) are also valuable tools to detect pulmonary masses or consolidation, thus increasing the diagnostic yield of transbronchial biopsy [71]. 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 receive a bronchoscopic examination and undergo a transbronchial biopsy, but only in less than half cases (30–50 %) is possible to reach an histological diagnosis without a surgical lung biopsy. **Broncho-alveolar lavage** (**BAL**) is an essential tool for differential diagnosis of subacute or chronic alveolar opacities, and seems to be valuable for the positive diagnosis of PPL. Differential diagnosis of pulmonary lymphoma includes viral, bacterial or opportunistic pneumonia, radio-induced and drug induced pneumonitis, tuberculosis, sarcoidosis, cryptogenic organizing pneumonia (COP), alveolar proteinosis, lipidic pneumonia, alveolar haemorrhage, bronchioloalveolar cell cancer, hypersensitivity pneumonitis, eosinophilic pneumonia, vasculitis, primary or metastatic lung tumors. Differential diagnosis is primary based on clinico-radiological 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 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) [70]. 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 [69].

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 **transparietal 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 [70]. When these less invasive procedures fail (in this happens especially in non MALT lymphomas) 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 characterised in fact by distinct molecular profiles that can be easily demonstrated on routine paraffin sections, and can be utilised 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 characterised 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 (CD5+, cyclina D1+) chronic lymphocytic leukaemia (CD5+, CD23+) [72]. Flow-cytometry can provide relevant information by revealing the presence of clonal B-cell populations characterised 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 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 [73]. 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 [74] with dissemination to lymph nodes (18 %) bone marrow (7 %) and for lung a simultaneous specific gastric localization o gastric relapse in 14 % of patients [75]

Treatment

Therapeutic options in primary NHL of the lung include the following strategies: watch and wait approach, surgery, chemotherapy, and chemotherapy followed by radiotherapy. There are no guidelines as to when surgery is indicated. Surgery for solitary lesions and adjuvant therapies for more extensive disease has been the general consensus. Overall 60–70 % of the patients with PLL are surgical candidates; however, incomplete resection is reported to be the case in more than 50 % of the cases. Combined modality therapy appears to be superior in patients with bulky disease, residual disease following operation and an unfavorable non-MALT type of histology. Anthracyclines-based chemotherapy with anti-CD20 monoclonal antibody seems to be optimal therapeutic strategy in patients with primary DLBCL of the lung.

Low grade lymphoma has been treated by chemotherapy, usually of a single alkylating or nonanthracycline-combination type. Lesions are commonly chemoresponsive and are also radioresponsive, although tolerance issues limit the applicability of radiation to limited regions of the lung. There is no indication that such treatments are curative, although prolonged survival is common.

MALT lymphoma. While pulmonary MALT lymphoma is a highly indolent disease, no standard approach for the management of such patients has been defined [76, 77]. While resection or, when surgery is at high risk, radiotherapy are still indicated for localized lesions, pulmonary MALT lymphomas often present in a multifocal fashion. Consequently, relapses appear to be common following localized treatment, arising the question whether upfront management with systemic therapy might be beneficial. In fact, chemotherapeutic approaches including various regimens have successfully been used. Various chemotherapies have been tested, including alkylanting agents such as cyclophosphamide or chlorambucil, the nucleoside analogs cladribine (2CdA) or fludarabine, the latter in combination with mitoxantrone as have combination regimens including cyclophosphamide, vincristine, and prednisone, or mitoxantrone, chlorambucil, and prednisone. Oxaliplatin (L-OHP) seems to be an other highly active agent. Low dose Thalidomide has been reported to be associated with a very good partial response. Long terms results, however, have to be awaited in view of the relatively short follow-up time in these series and the tendency of MALT lymphomas to recur, sometimes even after decades. In addition, some authors [78] reported that Rituximab as single agent is safe with significant activity in untreated or relapsed MALT lymphoma patients. Treatment with the anti CD20 antibody Rituximab has been reported also to transform the MALT lymphoma in a pure plasma cell tumour. Another potentially active class of anti-cancer agents drugs are those targeted to the inhibition of the NFkB pathway, the common target of the recurrence translocations. An example of this class is bortezomib that is currently being tested in clinical trials specifically designed for patients with MALT lymphoma. For most patients, course of the disease is indolent with an estimated 5-year survival at more than 80 %, but the risk of relapse seems to be constant with an estimated 5-year time to progression at approximately 35 %. Relapses may occur in the same pulmonary localization, but also in other mucosal or non-mucosal sites.

LYG; Aggressive B-cell and T-cell type lymphomas. LYG grade 1 and 2 are often treated with interferon alpha 2 b; cases in which steroids and/or cyclophosphamide were beneficial have been reported. Rituximab, associated to chemotherapy, has been shown to be efficacious in LYG- grade 3, and in PTLD monomorphic disorders and its promising in other forms of large B cell lymphomas. The B-cell lymphomas require chemotherapy or combined-modality therapy [79]. Despite such different therapies, however, systemic progression is still common, and relapse-free rates of approximately 40–50 % are expected. T-cell lymphomas have a poorer prognosis with 50 % mortality at 2 years even with combined modality treatment. In HIV patients highly active antiretroviral therapy is useful and in transplanted subjects reduction of immunosuppression is used with good results in less aggressive forms.

Secondary Lymphomas

Secondary lung localization by lymphomas occurs with relative frequency (up to 20.5 % at autopsy), with different patterns of infiltration (peribronchial/perivascular, nodular, alveolar, interstitial, pleural, endobronchial). The lymphangitic pattern is frequent in **B-cell lymphomas and leukaemia**, whereas the nodular and interstitial patterns are mainly

observed in Hodgkin's lymphoma and T/NK-cell lymphomas respectively [80].

The lungs are the most common site of visceral involvement in patients with **mycosis fungoides**. Radiographic manifestations can simulate pneumonia and herald a poor prognosis. Mycosis fungoides is an extranodal CD4+ T-cell lymphoma primarily affecting the epidermis, and it is not clear why the lungs represent a preferential target of secondary involvement, although it is possible to speculate that homing signals shared by epidermal and pulmonary microenvironments can attract the same subset of T-lymphocytes (similar to Langerhan's cell localisation in bronchiolar epithelium).

Radiological evidence of lung involvement can occur in 12 % of patients with **Hodgkin's lymphoma** at diagnosis. Radiological abnormalities can be caused by either secondary HL involvement or infective diseases, and the differential diagnosis is critical, so that surgical biopsy is often needed for a correct diagnosis.

When a lymphoma develops in neighbouring sites (e.g. mediastinal lymph nodes and thymus) the lungs can be directly infiltrated by neoplastic cells. Complications can be minimal or severe, depending on the type and amount of involvement. The lymphomas that more frequently invade the lungs from the mediastinum are of course those prevailing at that site, including Hodgkin's lymphoma classic type, primary mediastinal (thymic) large B-cell lymphoma, and T-cell lymphoblastic lymphoma. Primary mediastinal (thymic) large B-cell lymphoma (W.H.O. ICD-O code 9679/3) is characterised by peculiar clinical and biological features, and need to be distinguished by other DLBCL involving the lungs.

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32 Pulmonary Manifestations of Hematological Malignancies: Focus on Pulmonary Chronic Graft-Versus Host Disease

Karine Chagnon, Frédéric Schlemmer, Véronique Meignin, and Anne Bergeron

Introduction

Advances in the management of patients in terms of the diagnosis and treatment of hematologic malignancies and treatment-related complications, especially infectious complications, have increased survival time. However, more than half of the patients treated for hematologic malignancies will develop a pulmonary complication during their follow-up, infectious pneumonia remaining the most common diagnosis that should be considered first in regard to its potential severity. Otherwise, new complications that may involve different organs, including the lungs, have been increasingly reported. Currently, over a quarter of lung infiltrates occurring in the context of hematological diseases are due to noninfectious causes [1]. Thus, lung physicians may be increasingly confronted with these lung disorders. Various noninfectious pulmonary complications have been described in the different hematological malignancies; however, these complications are most often studied in the context of allogeneic hematopoietic stem cell transplantation (HSCT). In this chapter, we will briefly review the lung diseases associated with various hematological malignancies before focusing on noninfectious pulmonary complications following allogeneic HSCT.

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Pulmonary Manifestations of Hematological Malignancies

Given the wide spectrum of lung diseases that can occur in the context of hematological malignancies, the diagnostic process must be rigorous. In addition to the many pathogens potentially involved, a wide range of noninfectious causes should be considered. The pulmonary location of the hematological disorder should be considered depending on the underlying disease. Some hematological diseases, such as lymphoma, can progress in the lung, unlike others, such as myeloma, for which lung involvement is very rare. Pulmonary cardiogenic or noncardiogenic edema is frequent and can be due to hyperhydration required before chemotherapy, cardiotoxicity secondary to use of anthracyclines or increased capillary permeability from drugs such as all-trans-retinoid acid or cytosine arabinoside. Intra-alveolar hemorrhage is common in patients with thrombocytopenia or allogeneic HSCT. Many drugs frequently used for the treatment of hematological disorders may cause lung damage (Pneumotox.com); these drugs include Bleomycin, Busulfan, Chlorambucil, Cyclophosphamide, Cytosine, Fludarabine, Rituximab, Dasatinib and others (Table 32.1). Radiotherapy may cause radiation pneumonitis. Drug treatments can cause entirely different clinical patterns depending on the target organ in the respiratory system (lung, airways and pleura) [2].

Different other "immunological" causes of pneumonitis may occur in the course of several hematological malignancies (Table 32.2). For example, sarcoid-like granulomatosis may be associated with lymphoma, eosinophilic pneumonia may occur in the course of a myelodysplastic syndrome and pulmonary graft-versus host disease (GVHD) may be a complication following allogeneic HSCT. The medical history of the patient, including the clinical history of lung involvement and the type of underlying malignancy, the lung CT scan and the bronchoalveolar lavage (BAL), should be used when making a diagnosis. A lung biopsy, when possible, would rule out infection and would reinforce or even confirm a diagnostic

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Table 32.1 Main drugs used for the management of patients with hematological malignancies known to induce lung toxicities [2]

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
Immunomodulatory agents	Interferons, anti-Interleukin-2, TNF alpha inhibitors, Sirolimus, Temsirolimus
Monoclonal antibodies	Rituximab, Gemtuzumab ozogamicin, Alemtuzumab
Miscellaneous	Blood transfusion, GM-CSF, G-CSF

Table 32.2 Nonspecific noninfectious pulmonary complications reported in hematological malignancies

Hematological malignancies	Pulmonary complications
Acute leukemia	Organizing pneumonia [60]
	Sweet's syndrome [61]
	Alveolar proteinosis [62]
Lymphoma/chronic lymphocytic leukemia	Sarcoid-like granulomatosis [63, 64]
	Langerhans histiocytosis [65]
	Lung cancer [66, 67]
Myeloma	Amyloidosis [68]
	Venous thromboembolism [69]
Waldenstöm's macroglobulinemia	Intra-alveolar hemorrhage [70]
	Pulmonary edema [70]
	Amyloidosis [68, 70]
	Lung cancer [71]
Myelodysplastic/ myeloproliferative disorders	Extramedullary hematopoiesis [72]
	Sweet's syndrome [72]
	Diffuse infiltrative lung disease in the context of autoimmune disorders [72]
	Eosinophilic pneumonia [72]
	Alveolar proteinosis [72]
	Organizing pneumonia [72]
	Pulmonary hypertension [73]

hypothesis. However, it is rarely performed in this context because it is associated with significant mortality and morbidity and results in a definitive diagnosis in only 60 % of cases [3]. Furthermore, new biological tools including polymerase chain reaction for many pathogens and antigen for *Aspergillus* used on both respiratory samples and sera greatly help to diagnose an infection [4]. Finally, the overall diagnostic approach of lung infiltrates in patients treated for a hematological malignancy must take into account the possible overlapping of different infectious and/or noninfectious causes.

Pulmonary Manifestations of Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic HSCT is used as a curative treatment in various tumoral and non-tumoral diseases. The patient's abnormal hematopoietic tissue is replaced with healthy stem cells.

The transplanted stem cells can be derived from bone marrow, peripheral blood or umbilical cord blood harvested from a related donor or a compatible unrelated donor. Before the transplantation procedure is performed, the host is prepared with a special conditioning regimen that usually involves fractionated total body irradiation and cytotoxic chemotherapy to prevent graft rejection and to eradicate any residual tumor cells. Until recently, the conditioning regimen was "myeloablative," leaving the patient severely neutropenic for several weeks. Over the past few years, nonmyeloablative transplants have been developed based on the graft-versus leukemia/lymphoma principle, thereby eradicating residual tumor cells. The conditioning regimen for these transplants is attenuated, depressing only the host immune response and thus limiting the neutropenic period to just a few days. This means that allogeneic HSCT can now be extended to older and frailer patients with comorbidities who have had long-term treatment in the past, which has increased the number of allogeneic HSCT procedures performed. The major complications that occur after allogeneic HSCT are infections or the consequences of the immune reactions of GVHD, which can be either acute or chronic depending on the clinical features [5]. For unknown reasons, unlike the skin, gastrointestinal tract and liver, the lungs have not been identified as a target of acute GVHD in humans. In contrast, lung involvement is common in chronic GVHD that may be either restricted to a single organ or tissue or widespread. Chronic GVHD is characterized by tissue destruction resulting in fibrosis and is associated with a process in which donor T cells recognize peptides presented by the major histocompatibility complex on antigen-presenting cells of the host. GVHD targets epithelial cells of various organs with an incidence that depends on various factors and most commonly occurs during unrelated transplantations and peripheral stem cell transplantations. Treatment of GVHD requires the maintenance or enhancement of immunosuppressive therapy. The prognosis of GVHD is primarily related to the severity of the initial response to corticosteroids. The occurrence of chronic GVHD affects the morbidity, mortality and the quality of life of patients [6].

Chronic Pulmonary Graft Versus Host Disease

Chronic lung GVHD has been identified, the diagnosis of which is based on histopathological observations performed during lung biopsies showing bronchiolitis obliterans (BO). Although BO is the only condition attributed to pulmonary GVHD [5], other clinico-histological lung conditions are known to be associated with GVHD, such as organizing pneumonia (OP, formerly named bronchiolitis obliterans organizing pneumonia, BOOP) [5, 7]. Other noninfectious diffuse infiltrative lung diseases have been described and may also be associated with GVHD [8]. Although less frequent than BO, these diseases are often ignored, and their incidences may be underestimated.

Bronchiolitis Obliterans

Bronchiolitis obliterans (BO) is the main non-infectious late pulmonary complication in allogeneic HSCT recipients. This serious and potentially fatal complication typically develops in the first 2 years following transplant but also can occur several years later [9, 10]. The incidence of BO is difficult to assess; according to several retrospective studies, it varies from 2 to 26 % [11–16]. This disparity is mainly due to the lack of consensus regarding the diagnostic criteria. The most recent study, which was based on the largest number of patients, reported a prevalence of 5.5 % [15]. The incidence increased to 14 % in the subpopulation of patients who developed extrathoracic chronic GVHD [15]. Over a period of 3 years, we conducted a prospective cohort study that included a systematic follow-up of lung function for all of the consecutive patients who underwent an allogeneic HSCT in our center. Out of the 243 enrolled patients scheduled to be engrafted, 202 were included at Day 100, with an 18-month cumulative incidence of BO estimated at 12.9 % (Study NCT01219972 ALLOPULM clinical trials, analysis in progress; [17]).

Numerous risk factors for BO have been proposed in various retrospective studies, including age of the donor or recipient, type of transplant, degree of HLA incompatibility, presence of gastroesophageal reflux, gammaglobulin levels, type of GVHD prophylaxis, type of conditioning regimen, underlying blood disorder, tobacco use or acute GVHD, with conflicting results [8]. The only association reported in all of the studies was the occurrence of extrathoracic chronic GVHD at the time of BO diagnosis. One objective of our ALLOPULM study was to prospectively identify the events occurring within 3 months after transplantation that are associated with the subsequent occurrence of BO. Using multivariate analysis, we showed that a history of smoking, the occurrence of pulmonary infection, and pre-existing abnormal pre-transplant pulmonary function were associated with BO development [17].

Physiopathology of Bronchiolitis Obliterans

The exact pathogenesis of BO is still unknown. Epidemiological studies have shown an association between the development of BO and the presence of active chronic GVHD, which led to the hypothesis that BO is, in fact, chronic GVHD of the lung [18]. The most important mechanism contributing to BO would then result from the immune-mediated attack of airway epithelial cells by donor T cells. As opposed to acute GVHD, chronic GVHD also involves B-cell stimulation, autoantibody synthesis and systemic fibrosis [19]. Mouse models of chronic GVHD involve three disease mechanisms: autoantibody synthesis, pro-fibrotic processes and defective thymic function. Thymic damage leads to a decrease in T_{Reg} cell number and function and defective negative selection of T cells [19].

The recent development of an animal model of BO caused by allogeneic HSCT has revealed new pathophysiological pathways [20]: the peribronchiolar inflammatory infiltrate is mainly composed of CD4 lymphocytes, Clara cells that regenerate bronchiolar epithelium may be targets and a large number of cytokines are produced during the process [20]. More recently, the peribronchiolar deposition of alloantibodies was demonstrated in the same animal model, as was the role of mature B cells from the donor in the development of BO [21].

Some authors found that BO could be triggered by lower respiratory tract infections. In fact, it has been demonstrated that patients who present with respiratory syncytial or parainfluenza virus infection have an increased risk of developing BO in the year following HSCT [22]. The presence of a respiratory tract infection may lead to airway inflammation that causes an inappropriate alloimmune reaction.

Diagnosis of Bronchiolitis Obliterans

The definitive diagnosis of BO is pathologic. The National Institutes of Health Consensus proposed some histopathological criteria for BO based on a limited amount of original data [23]. The Pathology Working Group Report retained the presence of unequivocal dense eosinophilic scarring of the bronchioles resulting in some degree of luminal narrowing as a diagnostic (Fig. 32.1b). Inflammation is common but variable and insufficient for diagnosis [23]. In fact, Yousem et al. and Yokoi et al. published small pathological series in allogeneic HSCT recipients with chronic GVHD and lung involvement [24, 25] and reported different small airway abnormalities in this setting. Yousem et al. described two types of bronchiolar affections: lymphocytic bronchiolitis and cicatricial BO. Lymphocytic bronchiolitis is characterized by peribronchiolar/bronchiolar lymphocytic and plasmocellular infiltrate. Airway inflammation is predominantly lymphocytic and plasmocellular. Cicatricial BO is characterized by the obliteration of the airway lumen by dense fibrous tissue. The authors proposed that cicatricial BO is the

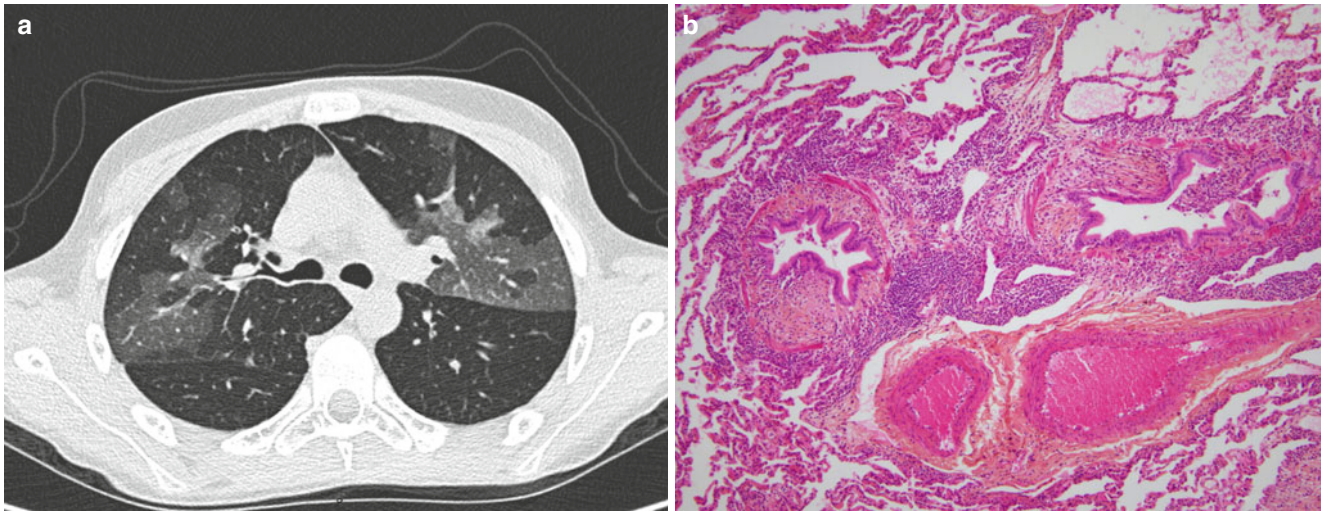

Fig. 32.1 Lung computed tomography (CT) scan (**a**) and lung biopsy (**b**) from a patient who was diagnosed with bronchiolitis obliterans 12 months after an allogeneic hematopoietic stem cell transplantation. The CT scan shows a mosaic pattern (**a**). The histological analysis shows a bronchiolar wall thickened by inflammatory fibrosis located between the epithelium and the smooth muscle. The airway lumen is narrowed (HES x 100) (**b**)

late-stage of lymphocytic bronchiolitis [24]. The pathologic description of Yokoi et al. comes from eight autopsy cases. Small airway lesions varied from early inflammatory changes to late scarring in each case. The inflammatory lesions were usually mild and mostly lymphoplasmacytic, except in three patients with predominant neutrophilic infiltrates. In all cases, inflammatory and scarring stages were present simultaneously [25]. Although the gold standard for diagnosis of BO is the demonstration of bronchiolar lesions upon histological evaluation of a lung specimen, it is not current practice to obtain a lung biopsy. Transbronchial biopsies have poor sensitivity, and surgical lung biopsies are invasive and usually reserved for cases of confusing diagnosis. Thus, BO is usually diagnosed as a new fixed airflow obstruction demonstrated by pulmonary function testing (PFT). BO syndrome (BOS) is diagnosed based on clinical, functional and radiological evaluation of the patient.

BOS clinically manifests as dyspnea at rest or on exertion, dry cough or wheezing. In a significant proportion of cases, it is asymptomatic and revealed by screening PFT. Clinical diagnoses of BOS are based on new-onset airflow obstruction identified by spirometry. Because BOS initial symptoms are nonspecific and spirometric findings are not sensitive, most patients are diagnosed when they have severe airway obstruction. PFT is not sensitive, as BOS is a distal airway disease, and bronchiolar obstruction needs to be widespread before FEV1 declines [26].

The currently used definition is that of the National Institute of Health (NIH) consensus guidelines for chronic GVHD, published in 2005: a 1-s forced expiratory volume (FEV1) value <75 % of that predicted and a FEV1/forced vital capacity (FVC) ratio <70 %, together with the exclusion of an infection and the presence of an extrathoracic sign of GVHD [5] (Table 32.3). However, some patients do not meet this functional criterion; despite the presence of BOS, the FEV1/FVC ratio may remain normal (>70 %). In fact, because BOS is a disease of the small airway, distal airway obstruction may lead to air trapping, thereby increasing the residual volume (RV). Consequently, the FVC declines concomitantly with the FEV1, and the FEV1/FVC ratio stays over 70 % [27]. NIH-BOS criteria include signs of air trapping, observed either by PFT (RV >120 %) or high-resolution computed tomodensitometry (HRCT) (Table 32.3). Recently, modification of these guidelines has been proposed [18]. To minimize the dynamic collapse of airways during the forced expiratory maneuver, Chien et al. proposed the use of slow vital capacity (SVC) instead of FVC for the diagnosis of airway obstruction. They also suggested that patients with annual FEV1 declines >5 % (from pre-transplant PFT) be considered at high risk of developing BOS and that an annual FEV1 decline >10 % (from pre-transplant PFT) be considered a diagnostic criterion for early BOS, even for a FEV1 >75 % of the predicted value [18]. Finally, two groups of patients may be diagnosed with BOS: one with a classical obstructive ventilatory defect and one with a normal FEV1/FVC ratio [18, 27]. The prognoses of both patients are similar [27]. Future studies should focus on the early detection of BOS. Chien et al. found that allogeneic HSCT recipients with annual FEV1 declines >5 %, even with FEV1/FVC ratios >80 %, have higher risks of nonrelapse mortality; this suggests that early airflow decline can be used as an indicator of early BOS [28]. This finding should prompt systematic

Table 32.3 Consensus Criteria for diagnosis of bronchiolitis obliterans/bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation

2005 NIH Consensus Criteria [5]	Proposed modified Consensus Criteria [17]
All the following should be met:	All the following should be met:
1. FEV1 < 75 % of predicted normal and FEV1/FVC <70 %.	1. FEV1 < 75 % of predicted normal.
2. Either signs of air trapping by PFT (RV >120 % of predicted normal) or signs of air trapping, small airway thickening or bronchiectasis by in- and expiratory HRCT or pathological confirmation of constrictive bronchiolitis.	2. FEV/VC <0.7.
3. Absence of active respiratory tract infection.	3. Evidence of air trapping on HRCT or RV >120 % of predicted normal.
4. In case of lacking histological proof of BO, at least one other distinctive manifestation of cGVHD in an additional organ system is required.	4. Absence of active respiratory tract infection. 5. Presence of active cGVHD in another organ than the lung. 6. Decrease of the FEV1 by at least 10 % since pretransplant. 7. Use of slow vital capacity for calculation of the FEV1/VC ratio.

FEV1 Forced expiratory volume in 1 s, *FVC* forced vital capacity, *PFT* pulmonary function testing, *RV* residual volume, *HRCT* high resolution computed tomography, *BO* bronchiolitis obliterans, *cGVHD* chronic graft-versus host disease

serial PFT after transplant, with careful attention to patients who develop airflow decline over time.

In addition to PFT, HRCT should be performed. In the case of BOS, it may reveal a mosaic pattern suggestive of air trapping (Fig. 32.1a) that can be accentuated on expiratory cuts. It can also reveal bronchial thickening, bronchiectasis or bronchiolar nodules with a tree-in-bud pattern [5, 29]. Otherwise, HRCT is needed in the initial evaluation of symptomatic patients to eliminate other causes of respiratory symptoms, such as infectious or inflammatory pneumonitis. Its value in the follow-up of a patient diagnosed with BOS is limited unless new respiratory symptoms develop. Finally, a bronchoscopic exam should be performed to rule out infection in the presence of infiltrates at the HRCT. In the case of normal imaging studies, nasal aspirates, sputum stains and cultures are considered sufficient to rule out viral, bacterial or fungal disease [5].

BOS may also occur after lung transplantation as the result of a chronic graft rejection. Philit et al. have shown very similar clinical, imaging and functional features both in lung transplant and allogeneic HSCT recipients [30]. Thus, the studies in each of these situations contribute to a better understanding of both conditions.

Management of Bronchiolitis Obliterans Syndrome

BOS is a potentially fatal complication. Despite advances in the management of allogeneic HSCT recipients, the survival and treatment of patients with BOS have not improved over the last two decades. The overall survival rates at 2 and 5 years after allogeneic HSCT are respectively 45 and 15 % in patients who develop BOS [26]. The natural history of BOS is variable. Classically, PFT declines with time, and patients develop infectious complications, which can lead to respiratory insufficiency and, eventually, death. Some patients remain stable after the development of airway obstruction, and a minority (20 %) will respond to treatment [31]. Actual management is based on case series and expert opinion. Based on the assumption that BOS is a manifestation of chronic GVHD, current practice involves optimizing or reintroducing immunosuppressive therapy upon a diagnosis of BOS. Some reports suggest that high-dose systemic corticosteroids (1–2 mg/kg) can improve or at least stabilize the FEV1. If BOS develops upon tapering the immunosuppressive therapy, clinicians usually reintroduce the tapered drug in combination with corticosteroids. Some case reports/series suggest other immunosuppressive therapies, such as TNF-receptor blockade, imatinib and extracorporeal photopheresis (ECP), may be efficacious [26]. These therapeutic options need to be studied further. Converging data suggest the ineffectiveness of rituximab for BOS treatment [32, 33].

It is well known that long-term exposure to corticosteroids, even at low doses, leads to significant complications. To minimize the morbidity associated with this treatment, considering the low efficacy of steroids in this setting, some authors have suggested alternative agents with anti-inflammatory properties. The use of topical steroid treatment is supported by two retrospective studies. We reported decreases in dyspnea and improvements in FEV1 in seven patients with new-onset airflow obstruction treated with combined inhaled therapy (budesonide-formeterol) [34]. Bashoura et al. reported stabilization or improvement in FEV1 in 16/17 BOS patients treated 3–6 months with high-dose fluticasone [35]. A recent study suggests bronchodilator responsiveness in BOS patients [36]. This information may support the inhaled combination therapy, including a long-acting bronchodilator and a corticosteroid, over an inhaled corticosteroid alone. The efficacy of azithromycin in the treatment of BOS following allogeneic HSCT is controversial [37, 38]. Finally, the efficacy of montelukast as a corticosteroid-sparing agent in the treatment of chronic GVHD had been suggested in a pilot study [39]. These three agents are actually under study in BOS patients following HSCT, either alone or in combination [40].

Non Infectious Infiltrative Lung Diseases

Non infectious infiltrative lung diseases (ILDs) occurring late after allogeneic HSCT are not uncommon, representing 12 % to more than 60 % of late-onset non-infectious pulmonary complications in large retrospective studies, including OP [41, 42]. In the largest retrospective studies, ILDs after allogeneic HSCT are mostly described as OP, interstitial pneumonia or idiopathic pneumonia syndrome (IPS) [41, 43, 44]. Whereas OP has been well described in a large study [7], limited data are available on other forms of infiltrative lung diseases following allogeneic HSCT.

Idiopathic Pneumonia Syndrome

Idiopathic pneumonia syndrome (IPS) was first defined in 1993 by an NIH expert committee as diffuse alveolar opacities following allogeneic HSCT after lower respiratory tract infection or cardiac failure was excluded. This definition was recently updated to include new microbiological diagnostic tools for the exclusion of infection, especially for newly described pathogens (Table 32.4) [45]. Thus, this syndrome regroups different clinical entities that can be classified according to the primitively attempted lung compartment: parenchyma (acute interstitial pneumonitis (AIP), acute respiratory distress syndrome (ARDS), OP, iatrogenic lung injury) or pulmonary blood vessels (engraftment syndrome, capillary leak syndrome, diffuse alveolar hemorrhage). IPS is thought to result from a variety of lung insults, including the toxic effects of HSCT conditioning regimens, immunologic cell-mediated injury, inflammatory cytokines, and occult pulmonary infections [45]. Peri-engraftment respiratory distress syndrome (PERDS) occurring within 5 days of engraftment after allogeneic HSCT represents a clinical subset of IPS that should be identified because of its specific clinical characteristics and because its responsiveness to corticosteroids can lead to a good prognosis [45]. PERDS is the result of non-cardiogenic pulmonary edema with or without concurrent pleural effusions in the context of a diffuse capillary leak syndrome and dysfunction of other organs, such as the liver, kidney, skin or gut [45, 46].

Table 32.4 Diagnostic criteria of idiopathic pneumonia syndrome occurring after hematopoietic stem cell transplantation [42]

1. Evidence of w*idespread alveolar injury*
Multilobar radiologic infiltrates (chest X-ray, computed tomography)
Symptoms and signs of pneumonia (cough, dyspnea, tachypnea, rales)
Evidence of abnormal pulmonary physiology
Increased alveolar to arterial oxygen difference
New or increased restrictive pulmonary function test abnormality
2. *Absence of active lower respiratory tract infection*
Negativity of exhaustive microbiological assessments of BAL fluid and non-invasive samples (serum, nasal swab, sputum)
Bacteriology, virology, mycology and parasitology
Culture, cytology, direct fluorescence, serology and polymerase chain reaction
Transbronchial biopsy if condition of the patient permits
3. *Absence of cardiac dysfunction, acute renal failure, or iatrogenic fluid overload as etiology for pulmonary dysfunction*
Conditions routinely included under the classification of idiopathic pneumonia syndrome
Pulmonary parenchyma
Acute interstitial pneumonitis
Acute respiratory distress syndrome
Organizing pneumonia
Delayed pulmonary toxicity syndrome
Vascular endothelium
Peri-engraftment respiratory distress syndrome
Noncardiogenic capillary leak syndrome
Diffuse alveolar hemorrhage

The incidence of IPS may vary according to the time following allogeneic HSCT and the type of conditioning regimen, with a historical reported incidence of 3–15 % after myeloablative conditioning, which may be lower (but with a similar severity) after nonmyeloablative conditioning [47]. Although time from allogeneic HSCT is not a diagnostic criterion of this syndrome, IPS occurs early in the course of HSCT (median time: 3–7 weeks after HSCT), with a historical high mortality rate (60–80 %, depending on the study, and up to 90 % in case of respiratory failure requiring mechanical ventilation). Proposed risk factors of IPS include total body irradiation-based myeloablative conditioning regimens, older recipient age, myelodysplastic syndrome, acute leukemia as an underlying disease and acute GVHD [45]. However, the association between IPS and acute GVHD is inconstant in humans, although a causal relationship between the two disorders has been proposed [45].

Therapeutic strategies for IPS include supportive care measures, broad-spectrum antimicrobial agents and intravenous corticosteroids. However, new treatments are needed due to the lack of efficacy of the currently applied strategies. Etarnercept, a neutralizing agent of TNF-α, is currently being evaluated for this indication and has yielded encouraging results that should be confirmed [48]. In fact, new insights in the classification of IPS that include very different entities would likely lead to better propositions of treatments.

Organizing Pneumonia

Organizing pneumonia (OP) is a distinct entity of diffuse ILD defined histopathologically by intra-alveolar connective tissue plugs of granulation tissue consisting of intermixed myofibroblasts and connective tissue that fill the lumens of the distal airways and extending into the alveolar ducts in association with chronic interstitial inflammation [49] (Fig. 32.2b). OP can occur in many different contexts: post-infection; following environmental, professional or toxic exposure; iatrogenically (due to medications, chemotherapy

or radiotherapy); or associated with connective tissue diseases, other chronic inflammatory diseases, solid cancers, hematological malignancy, lung transplantation or allogeneic HSCT. When no specific cause is found, OP is referred to as cryptogenic (COP). For more clarity, the terminology "Bronchiolitis Obliterans with Organizing Pneumonia (BOOP)" has been progressively abandoned because the major histological process is OP, whereas bronchiolar lesions are a minor and inconstant process [49]. The change in terminology is particularly relevant in the context of allogeneic HSCT to avoid confusion with BO, for which the clinical presentation and prognosis are very different.

In a case control study, Freudenberger et al. described 49 cases of biopsy-proven OP following allogeneic HSCT and compared them to control subjects from a computerized database of all patients who received an allogeneic transplant [7]. They identified a strong association between OP and previous signs of acute and chronic GVHD, suggesting a causal link between both entities [5, 7]. Other authors have also associated post-allogeneic HSCT OP with the presence of HLA B35 antigen [50]. The time from HSCT to OP onset ranged from a few days to more than 7 years, with a median time of 108 days. In 22 % of these cases, a tapering of immunosuppressive treatments preceded the respiratory signs. The clinical presentation was similar to that of COP, mimicking unresolved or subacute infectious pneumonia with unspecific symptoms (fever, dyspnea and cough) and physical signs (crackles). Radiological signs consisted of alveolar, nodular or interstitial opacities with a focal, multifocal or more diffuse extension that is indicative of the diagnosis when the topography of the lesions is peripheral or peribronchovascular [7, 51, 52] (Fig. 32.2a). Unlike COP, opacities were rarely migratory [7].

Freudenberger et al. found normal PFT in 38 % of the patients with post-allogeneic HSCT OP, whereas 43 % had a restrictive pattern, 11 % had an obstructive ventilatory defect and 8 % had both. In addition, a decrease in the carbon monoxide diffusion capacity was noted in 64 % of the cases [7]. The histological features of post-allogeneic HSCT OP were similar to the histological pattern of COP. In Freudenberger's study, almost 80 % of the patients were treated with steroids, with improvement or stabilization in most cases. However, 22 % of the patients progressed, despite a treatment with high-dose corticosteroids, leading to death due to respiratory failure in most cases [7].

Other Infiltrative Lung Diseases

In addition to OP, other ILDs are generally poorly described and are usually referred to IPS if diagnosed early after allogeneic HSCT or interstitial pneumonitis without more precision in these studies. In most cases, ILDs are associated with a history of extrathoracic acute and/or chronic GVHD and usually occur following the tapering of immunosuppressive therapy, mostly within the first 2 years after allogeneic HSCT [53]. These findings raise the hypothesis of pulmonary patterns of chronic GVHD. Very few data regarding lung histological patterns of ILD post-allogeneic HSCT are available because lung biopsies are rarely performed in this setting. However, diffuse alveolar damage, lymphoid interstitial pneumonia, nonspecific interstitial pneumonitis (Fig. 32.3) and eosinophilic pneumonia have been previously identified [24, 53–57]. Due to the difficulties of achieving lung biopsies in these patients and the current lack of impact of lung biopsy results on the management of patients in a noninfectious context, we reviewed 40 cases of ILD post-allogeneic HSCT and described their

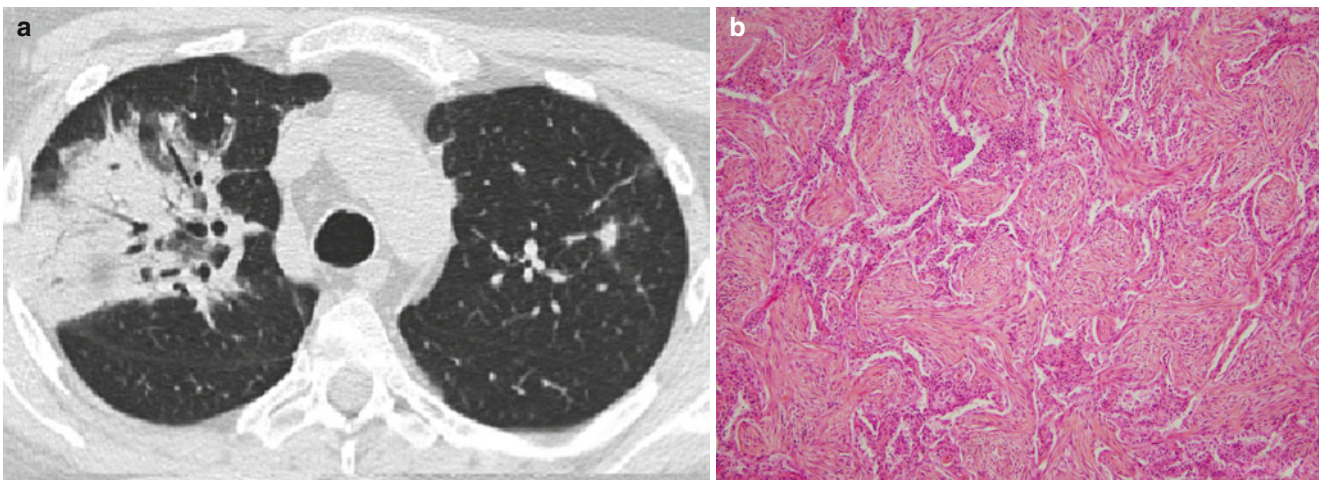

Fig. 32.2 Lung computed tomography (CT) scan (**a**) and lung biopsy (**b**) from a patient who was diagnosed with organizing pneumonia 8 months after an allogeneic hematopoietic stem cell transplantation. The CT scan shows an alveolar condensation (**a**). On lung biopsy, all the alveolar spaces are filled by fibroblast plugs (HES x 100) (**b**)

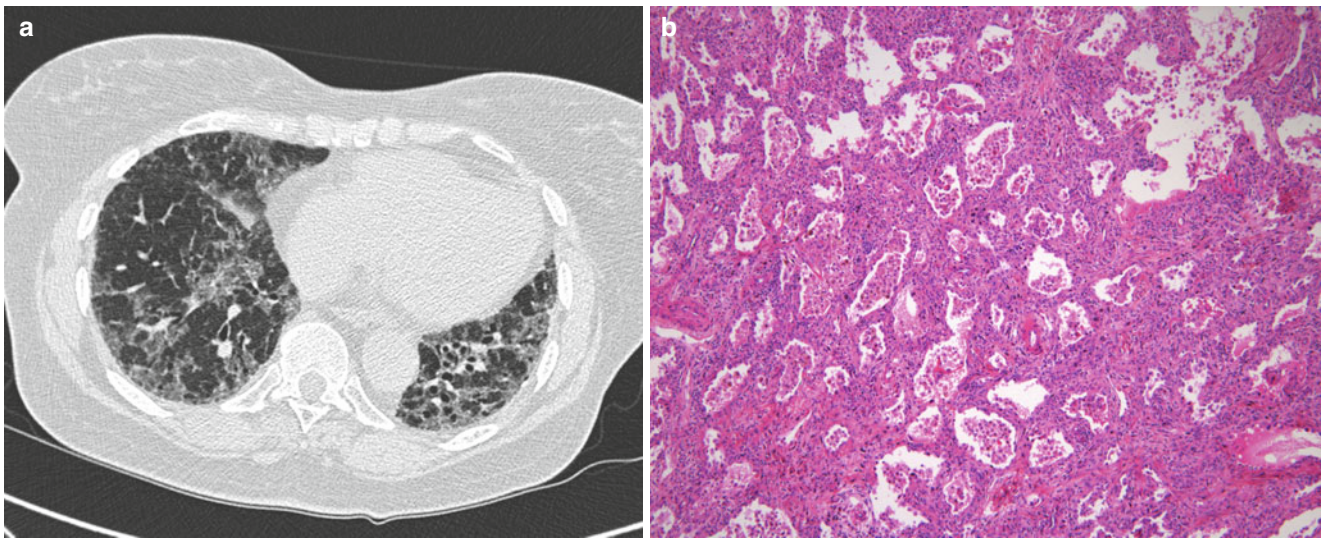

Fig. 32.3 Lung computed tomography (CT) scan (**a**) and lung biopsy (**b**) from a patient who was diagnosed with non specific interstitial pneumonia 4 months after an allogeneic hematopoietic stem cell transplantation. The CT scan shows diffuse ground glass opacities (**a**). The alveolar septa are uniformly thickened by inflammation and fibrosis (HES x 100) (**b**)

clinical characteristics and outcomes as it is usually done for idiopathic ILD [53]. The median time from allogeneic HSCT to ILD was 11.1 months (IQR, 9.1–19.2 months). The clinical presentation was unspecific, with cough (productive or not), variable levels of dyspnea and fever in half of the cases. As for IPS, infection had to be ruled out to retain the diagnosis of ILD. Radiological signs of ILD were variable in extent and ranged from localized to more or less diffuse (Fig. 32.3) [53]. BAL fluid analysis typically showed lymphocytic or both lymphocytic and neutrophilic alveolitis. In some cases, BAL can show an eosinophilic alveolitis that allows the diagnosis of eosinophilic pneumonia [55]. Pulmonary function tests usually showed a restrictive ventilatory defect associated with an alteration in the carbon monoxide diffusion capacity. PFT could also reveal an obstructive lung disease, isolated or not, suggestive of an overlap or a continuum between ILD and BOS [53].

High-dose steroids were usually administered as the first-line therapy and were often associated with a reinforcement of other immunosuppressive drugs. The survival rate was estimated to be 61 % at 24 months from ILD diagnosis. The main cause of death was respiratory failure [53]. Because late fibrosis often remains inaccessible to conventional therapies, early identification and treatment of ILD are essential for prognosis. For this purpose, ILD should be suspected in every atypical, subacute or unresolved case of infectious pneumonia, especially in the presence of extrathoracic chronic GVHD.

GVHD sometimes has features resembling autoimmune disorders, such as scleroderma, Sjögren syndrome, lupus erythematous, mixed connective tissue disease, polymyositis ANCA-positive vasculitis, or primary biliary cirrhosis. A spectrum of pulmonary manifestations occurring in patients with a well-defined connective tissue disease (CTD) after allogeneic HSCT similar to idiopathic CTD has been reported [54]. Therefore, nonspecific interstitial pneumonia and lymphoid pneumonia have been reported in the course of Sjögren-like disorders diagnosed on both clinical and biological characteristic features [54]. The incidence of these CTDs that may arise very late after allogeneic HSCT remains unknown, and they are most likely overlooked [54]. Several pathologic mechanisms have been proposed for these autoimmune manifestations, such as genetic predisposition, thymic deficiency, the expression of an abnormal B-cell and/or T-cell reconstitution or donor-related pathogenic clone transfer [58, 59]. The prognoses for these ILDs occurring in post-allogeneic HSCT connective tissue disorders are poor with very high mortality rates despite the usual administration of high dose steroids [54]. Considering therapeutic protocols similar to those used in CTD (e.g., cyclophosphamide, anti-CD20 monoclonal antibodies or TNFR blockers) might be interesting in addition or as an alternative to the more classical steroid therapy.

Conclusion

A wide spectrum of lung diseases can be observed in patients treated for hematological malignancies. In addition to infectious causes, various inflammatory conditions may be encountered similar to those observed in other contexts. In the context of allogeneic HSCT, these pulmonary complications are often attributed to GVHD. However, pulmonary GVHD is not a clinical diagnosis; rather, it is

only the concept of a pathophysiological process. The elucidation of specific clinical, radiological and histopathological pulmonary entities is necessary to adapt patient care and to improve prognosis.

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Pulmonary Hypertension in Orphan Lung Diseases

33

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Introduction

In the ERS/ESC (European Respiratory Society/European Society of Cardiology) guidelines for the diagnosis and the treatment of Pulmonary Hypertension, PH has been defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest as assessed by right heart catheterisation [1]. Precapillary PH (defined by normal pulmonary capillary wedge pressure) 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 33.1). 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 remodelling due to chronic hypoxemia [2]. 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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Classification of Pulmonary Hypertension

The classification of PH adopted in the ERS/ESC guidelines and recently revised during the 5th Word symposium on PH is presented in Table 33.1 [1, 3]. 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 diseases, HIV infection, portal hypertension, congenital heart disease, schistosomiasis). A sub-group 1′ includes a rare entity characterized by a predominant pulmonary venous or capillary involvement: pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH). Pathologic and genetic studies have recently demonstrated that PVOD and PCH represents distinct naming of the same entity [4–8]. Group 2 includes post-capillary PH due to left heart diseases, defined by an increased pulmonary capillary wedge pressure (above or equal to 15 mmHg). Group 3 was defined as "PH due to chronic lung diseases and/or hypoxia". In this group, the

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Table 33.1 Updated clinical classification of pulmonary hypertension

1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable
1.2.1. BMPR2
1.2.2. ALK1, endoglin, SMAD9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drug- and toxin-induced
1.4 Associated with
1.4.1. Connective tissue diseases
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1′. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
1′′. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension due to left heart disease
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
3. Pulmonary hypertension due to lung diseases and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. PH with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders splenectomy
5.2 Systemic disorders, sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure

Adapted from [1, 3].

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. 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 [9]. Group 4 defined chronic thromboembolic pulmonary hypertension. Group 5 corresponds to heterogeneous conditions with unclear or multifactorial etiologies. This group includes notably sarcoidosis, pulmonary Langerhans' cell histiocytosis, lymphangioleiomyomatosis, and neurofibromatosis type 1.

In the evaluation of PH occuring 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 risk factors of PAH (connective tissue diseases, portal hypertension, HIV infection…). Of note, precapillary PH associated with orphan lung diseases may be observed in different subgroups of this classification: in group 3 (syndrome of combined pulmonary fibrosis/emphysema), group 5 (sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis) and group 1′ (PVOD/PCH).

Pulmonary Hypertension Associated with Sarcoidosis

Sarcoidosis is a multisystem disease characterized by granulomatous inflammation of unknown cause, with pulmonary involvement being one of the commonest disease manifestations. PH may complicate sarcoidosis with an estimated prevalence of 1–28 % [10–13]. Pathological processes underlying sarcoidosis-associated PH (SAPH) are complex and multiple [10], and may fall under different groups according to the current clinical classification of PH [3]. A true vasculopathy with arterial or venous infiltration by granulomas may occur, generating venular lesions mimicking PVOD (Fig. 33.1) [14–16]. Cardiac sarcoidosis may contribute to post-capillary PH, mainly through diastolic dysfunction (myocardial involvement) [17]. 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 [10, 13, 17]. Enlargement of intrathoracic lymph nodes or fibrosing mediastinitis can lead to extrinsic compression of the proximal pulmonary vasculature [14, 18, 19]. Furthermore, hepatic involvement may exceptionally result in porto-pulmonary hypertension [20]. The often multifactorial nature of SAPH is best considered under a specific subgroup in the classification of PH – "unclear and/or multifactorial etiology" [3] (Table 33.1).

Although PH is frequently associated with advanced fibrotic lung disease in sarcoidosis [10, 15, 21], 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 [10, 14]. In absence of parenchymal involvement, distal granulomatous vasculopathy should be suspected [13–17, 22, 23]. Notably, pulmonary venular involvement have been frequently reported [14].

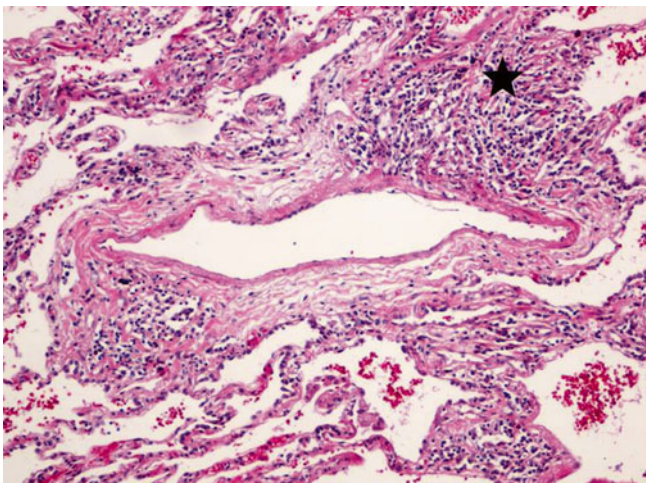

Fig. 33.1 Pathologic assessment of a patient with pulmonary hypertension associated with sarcoidosis. Pulmonary venous involvement is frequently observed in pulmonary hypertension associated with sarcoidosis. Epitheloid giant-cell granulomas (*) can be observed in the vicinity of veins, and may lead to their obstruction. Magnification 100, hematoxylin-eosin staining

Prevalence of PH in sarcoidosis patients vary largely according to the population studied. It has been estimated to be around 5–15 % in unselected patients with sarcoidoisis, up to 50 % in patients with persistent dyspnea [8, 14, 16, 22, 24] and as high as 75 % in patients with advanced parenchymal lung disease on transplantation waiting list [12]. 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 [17]. Several studies have demonstrated a correlation between severity of the disease and PH occurrence, in particular for mild or moderate PH [10, 12, 21]. Moreover, PH in sarcoidosis has been associated with oxygen desaturation during 6 min walking test and low DLCO [17]. However, PH may be present in all stages of sarcoidosis [10, 14] and referral for formal RHC is mandatory if PH is suspected [17]. 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 [25].

It is recognized that patients with SAPH have a worse prognosis compared to those without pre-capillary PH [21]. Five-year survival in SAPH has been estimated to be 59 %. Risk factors associated with mortality include high level of mPAP, African American ethnicity and chronic respiratory failure requiring oxygen therapy [26].

Oxygen therapy should be prescribed if chronic hypoxaemia is present to prevent hypoxic vasoconstriction. The efficacy of immunosuppressive therapy on pulmonary vascular disease in sarcoidosis is not clear [13, 27, 28]. The use of PAH specific therapy in SAPH has predominantly been assessed in open-label observational studies [24, 29–32]. However, a recent multicenter, double-blind, randomized trial comparing bosentan versus placebo in 35 patients with sarcoidosis and concomitant precapillary PH showed improvements in hemodynamics (mPAP and pulmonary vascular resistance), but no effect on exercise capacity (6MWD) or functional class in patients treated with bosentan [33]. A recent meta-analysis of available studies of specific therapies in SAPH confirmed these data [34]. Gas exchange deterioration may also occur following vasodilator therapy via uncoupling of hypoxic pulmonary vasoconstriction, resulting in worsening of ventilation/perfusion mismatch [35]. Furthermore, potential risk of pulmonary edema can occur in cases with predominant venular involvement in a manner similar to PVOD [24, 36]. 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 centres.

Finally, because of the poor prognosis of SAPH and the lack of efficacy of specific PAH therapy, lung transplantation should be considered earlier 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 [26] and primary graft dysfunction [37].

PH Associated with Pulmonary Langerhans' Cell Histiocytosis

Langerhans' cell histiocytosis is a systemic disease characterized by abnormal proliferation and infiltration of organs by Langerhans' cells. Pulmonary Langerhans' cell histiocytosis (PLCH) is a rare cause of diffuse parenchymal lung disease and occurs principally in smokers. PH can complicate the course of PLCH and severe PH is frequently reported in advanced disease [38–40]. Prevalence of severe PH (defined by mPAP ≥35 mmHg) in PLCH patients referred for lung transplantation assessment has been reported to range from 44 to 100 % [38, 39] significantly higher than other chronic lung diseases such as COPD or IPF [38]. Histopathological studies have shown a specific and diffuse pulmonary vasculopathy which predominantly involves the pulmonary veins and, to a lesser extent, the muscular pulmonary arteries (Fig. 33.2) [38]. Widespread pulmonary vascular lesions are present in the majority of PHLC related PH. Uncommonly, vascular lesions are due to direct infiltration by Langerhan's cells [38]. Pulmonary vascular involvement is usually characterized by a proliferative vasculopathy with intimal fibrosis and medial hypertrophy involving the small to medium-sized pulmonary arteries and septal veins. Notably, significant venous involvement with a "veno-occlusive pattern" is present in up to one third of patients [38]. Vascular lesions may be observed in areas free from parenchymal lesions [38, 41].

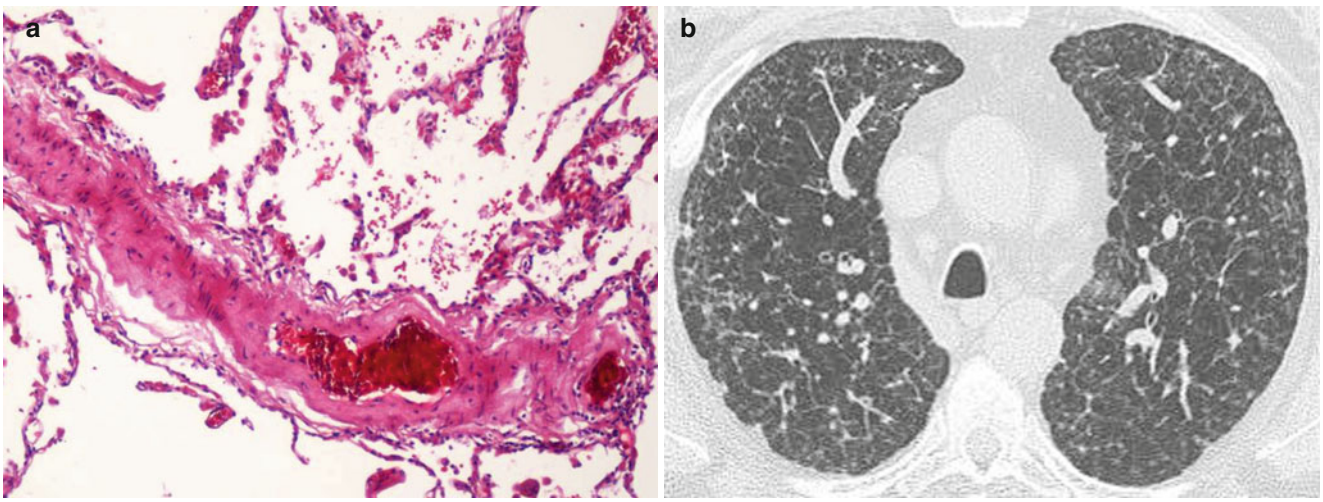

Fig. 33.2 Pathologic assessment and high-resolution CT of the chest of a patient with pulmonary hypertension associated with pulmonary Langerhans' cell histiocytosis. (**a**) Diffuse pulmonary vasculopathy which predominantly involves the pulmonary veins and, to a lesser extent, the muscular pulmonary 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

Discrepancy between hemodynamic severity and lung parenchymal involvement is frequently observed in PLCH related PH. Indeed, hemodynamic parameters and pulmonary function tests are not correlated, suggesting that a specific pulmonary vascular involvement occurs independently of parenchymal lesions [38]. Hemodynamic impairment appears to be the main source of exercise limitation in PLCH related PH [42]. In a retrospective study of 29 patients with PLCH related PH, Le Pavec et al. [43] demonstrated severe haemodynamic impairment with 66 % of subjects displaying a mPAP ≥40 mmHg. 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 increased 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 [43]. 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 [38, 41, 44]. Lungs or heart-lung transplantation remains the treatment of choice for end-stage PLCH and/or for severe PLCH related PH [39]. Of note, recurrence of PLCH in lung allografts has been reported and risk of recurrence was associated with the presence of extra-pulmonary disease prior to transplantation [39].

PH in Combined Pulmonary Fibrosis and Emphysema Syndrome

Combined pulmonary fibrosis and emphysema (CPFE) is a syndrome characterized by diffuse destruction of the lung parenchyma resulting from the combined effects of lung fibrosis predominant in the lower lobes and emphysema in the upper lobes [9, 45, 46]. 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. CPFE is classified in sub-group 3.3 "*Other pulmonary diseases with mixed restrictive and obstructive pattern*" (Table 33.1) [3]. CPFE is frequently associated with precapillary PH, usually with severe hemodynamic impairment [47–49]. 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. The prevalence of PH in CPFE has been estimated to be 50 % in a retrospective study using echocardiography [46]. A retrospective study reported the haemodynamic, functional and survival characteristics of 40 patients dysplaying PH associated with CPFE [50]. At the time of diagnosis, right heart catheterization revealed moderate to severe PH (mPAP of 40±9 mmHg, pulmonary vascular resistance of 521±205 dyn·s^{-1}·cm^{-5}, and cardiac index of 2.5±0.7 L.min^{-1}.m^2). Furthermore, 85 % of the patients were in either functional class III or IV, with a mean 6 min walking distance of only 244±126 m. Prognosis was poor with 1-year survival estimated at 60 %. Univariate analysis found that DLCO <22 %, pulmonary vascular resistance >485 dyn/s/cm^5, and

cardiac index <2.4 L/min/m^2 were predictive factors of death [50]. Interestingly, CPFE could also be present in connective-tissue diseases, with a similar prevalence of PH [51].

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 [35]. 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

Neurofibromatosis type 1 (NF1), also known as Recklinghausen's disease, is a genetic disease, with an incidence of 1:2,500 births that has a typical clinical diagnosis: neurofibromas, cafe-au-lait spots, lentigines and squelletal lesions [52]. The respiratory involvement is rare and is almost exclusively represented by kysts, bulae or interstitial infiltrates that can go up to pulmonary fibrosis [52]. Initially pulmonary hypertension has been described as a consequence to an advanced parenchymal disease, but evidence show that in patients with minimal parenchymal involvement there is a plexiform pulmonary arteriopathy similar to that observed in idiopathic PAH [53, 54–57]. Recently we identified and published a series of 8 cases of NF1 associated PH, in patients with mild or absent lung parenchymal abnormalities [58]. These patients developed PH late in the course of NF1, with a median age at diagnosis of 62 years (range 53–68 years). Although in NF 1 the sex ratio is 1, there was a clear female predominance in NF 1 PAH patients as in idiopathic and heritable PAH. At time of diagnosis they had severe clinical, functional and hemodynamic impairment. Of the 8 reported cases, 3 had no significant lung involvement on HRCT. Spirometry was normal in 5 patients with DLCO markedly decreased in all patients as a sign of pulmonary vascular involvement. Lung transplantation was performed in one patient displaying severe parenchymal disease with diffuse interstitial fibrosis and widespread cystic changes. Pathologic assessment of explanted lungs confirmed interstitial fibrosis with partial loss of parenchymal architecture, but also showed pronounced pulmonary arterial remodeling (Fig. 33.3) [58]. For the patients in our cohort and the other case reports response to specific PH therapy was poor, which resulted in a global poor outcome [57–59].

In conclusion after all these new data, NF 1 related PH was put in group 5 in the updated clinical classification of pulmonary hypertensions, along other forms of PH with unclear/multifactorial mechanisms [60]. 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

Lymphangioleiomyomatosis (LAM) is a rare multisystem disorder predominantly affecting women in their reproductive years [61]. It may occur sporadically with a prevalence of 1/400.000 adult females or in about 30 % of patients in the setting of tuberous sclerosis complex [61, 62]. LAM is

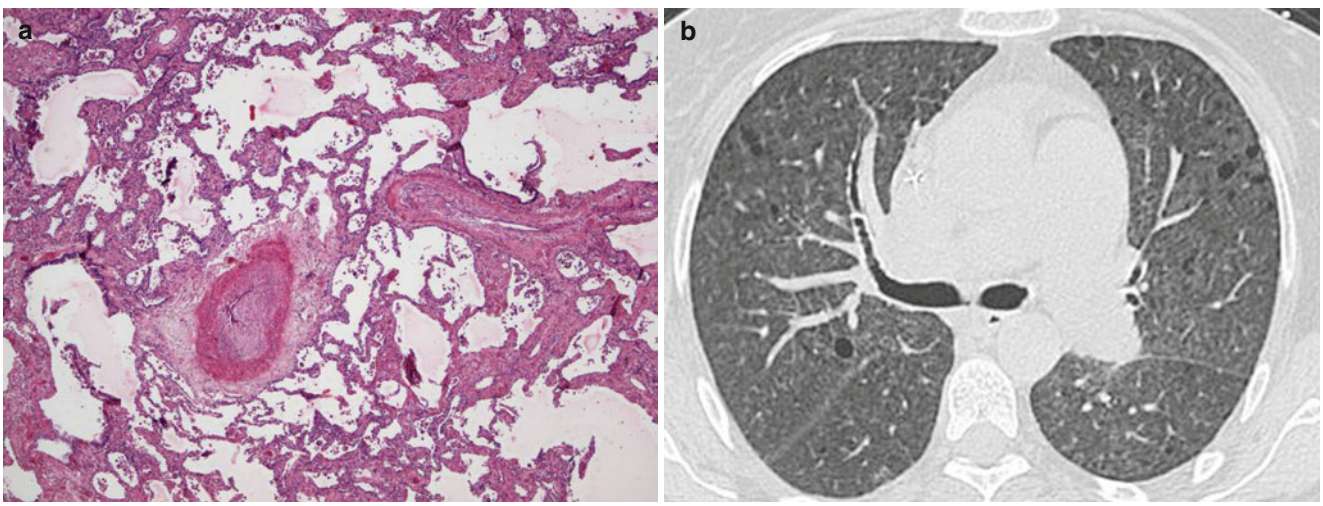

Fig. 33.3 Pathologic assessment and high-resolution CT of a patient with NF1-associated pulmonary hypertension. (**a**) Interstitial fibrosis with partial loss of parenchymal architecture associated with pronounced arterial remodeling complete occlusion by intimal fibrosis. Magnification 40, hematoxylin-eosin staining. (**b**) High-resolution CT of the chest showing diffuse small rounded lung cysts

characterized by 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 tumours, pleural and peritoneal chylous effusions and abdominal lymphangioleiomyomas [62, 63]. 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 [61–64]. The current accepted model for LAM is consistent with Knudson's "Two-hit" hypothesis of tumour 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 [65]. A major role of the complex hamartin-tuberin is to inhibit mTOR, implicated in cell growth, indeed the mutation in both TSC1 and TSC2 induces activation of mTOR [62]. Recently, sirolimus, a mammalian target of rapamicyn (mTOR) inhibitor has been shown to slow the rate of lung function decline [66]. But even with all these new and promising data, lung transplantation remains the only option for patients with advanced respiratory disease [61, 67–69]. In the latest clinical classification of pulmonary hypertension, PH associated with LAM is included in group 5 with unclear multifactorial mechanisms [3]. 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 [70]. 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 [71, 72].

Different studies evaluated the prevalence and characteristics of LAM related PH. By using cardiac echography with PH being defined as a systolic pulmonary arterial pressure >35 mmHg, Taveira-Dasilva et al. reported 8 cases of LAM related PH from 120 patients screened (prevalence 6.6 %) [70]. In a series of LAM patients referred for lung transplantation, by using right heart catheterization, Reynaud-Gaubert et al. found precapillary PH in 9/20 patients (prevalence 45 %) [67]. Based on these studies, the recent 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 [61]. However, it was suggested that estimation of PAP should be performed in patients considered for lung transplantation [68].

In the most recent retrospective multicenter study, Cottin et al. reported 20 patients with LAM and precapillary PH confirmed by right heart catheterization [73]. The mean age at diagnosis of PH was 49 years with a mean time interval between LAM and PH diagnosis of 9.2 years [73]. Hemodynamics showed moderate PH with a mPAP of 32 ± 6 mmHg, a cardiac index of 3.5 ± 1.1 $l \cdot min^{-1} \cdot m^{-2}$ and pulmonary vascular resistance of 376 ± 184 $dyn \cdot s \cdot cm^{-5}$, with only 4 patients (20 %) having a mean PAP > 35 mmHg [73]. These hemodynamic results suggested that in the majority of cases, PH was mild or moderate and related to the severity of pulmonary involvement [73]. Pulmonary function tests showed a decreased FEV1 at 42 ± 25 % and DLCO at 29 ± 13 % with blood gases showing mild hypoxemia (PaO2 of 7.4 ± 1.3 kPa in room air) [73]. Only 6 patients received oral PAH specific therapy and showed a decrease in m PAP and pulmonary vascular resistance from baseline. The authors showed that the overall probability of survival at 2 years was 94 % [73].

In conclusion, mild to moderate PH is relatively a common finding in LAM patients with severe lung involvement with chronic hypoxemia and pulmonary capillary destruction caused by cystic lung lesions probably may represent the predominant mechanism of PH in this setting. Nevertheless, some patients may have specific pulmonary vascular involvement, and one potential mechanism may be the activation 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

Hereditary hemorrhagic telangiectasia (HHT) is characterized by mucocutaneous telangiectases, recurrent epistaxes, macroscopic arteriovenous malformations (particularly in the pulmonary, hepatic, and cerebral circulation) and more rarely PAH. 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 activin receptor-like kinase-1 (*ACVRL1* or *ALK-1*) located on chromosome 12, *endoglin* on chromosome 9. *ACVRL1* and *endoglin* genes are involved in the transforming growth factor-ß (TGF-ß) signalling pathway as *BMPR2* gene, the main predisposing gene of heritable PAH. Indeed, proteins encoded by *BMPR2* and *ACVRL1* genes, form an heteromerix complex, associated with endoglin [74].

Several mechanisms may lead to PH in HHT patients. Arteriovenous malformations may create clinically significant right-to-left shunts, causing hypoxemia, paradoxical embolism, stroke, and cerebral abscesses [75–79]. PH may develop as a consequence of a hyperkinetic state resulting in heart failure associated with high cardiac output. However, HHT is also associated with PAH characterized by remodeling of small pulmonary arteries, with broadly similar histologic lesions than observed in idiopathic PAH [79–81]. Many case series have reported the association of *ACVRL1* mutations and PAH in HHT patients without any other cause

of PH [80–85]. 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 [82, 83, 86]. 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 [80]. 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 [80]. In conclusion, the absence of HHT clinical manifestation in PAH patients should not exclude the diagnosis of PAH associated with *ACVRL1* mutation and a detailed familial history and a careful examination of PAH patients and first-degree relatives for stigmata of HHT may help detect these patients.

Pulmonary Veno-Occlusive Disease

Pulmonary veno-occlusive disease (PVOD) and pulmonary capillary hemangiomatosis (PCH) are uncommon forms of PH difficult to diagnose [87]. It has been suggested that PVOD represents 5–10 % of histological forms of cases initially considered as idiopathic PAH [5, 6, 88, 89]. Whereas idiopathic PAH shows a distinct female preponderance, PVOD is characterised by a higher male/female ratio [6]. Initially, PVOD and PCH were placed in two different groups, both distinct from PAH. 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. 33.4), and localized capillary proliferations which could obstruct veins and venular walls in PCH [8, 90]. Similarities in pathological features and clinical presentation suggested that PVOD and PCH may be two presentations of the same disease. According of these observations

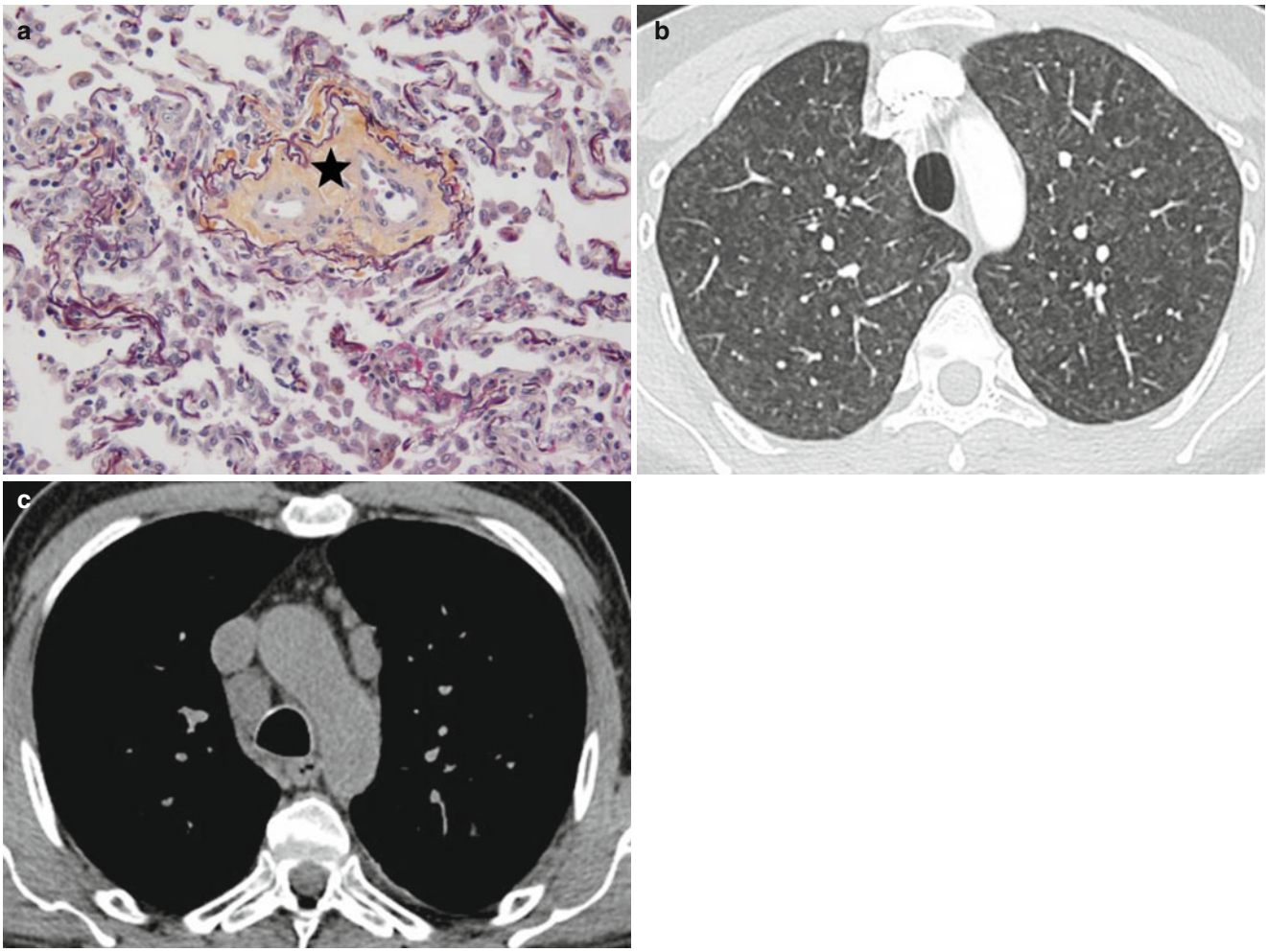

Fig. 33.4 Pathologic assessment and high-resolution CT of a patient with pulmonary veno-occlusive disease. (**a**) Fibrous obstruction of a septal vein (*) associated with capillary proliferation. Magnification 400, hematoxylin-eosin staining. (**b**) High-resolution CT of the chest showing diffuse poorly-defined centrilobular nodular opacities with associated septal line thickening. (**c**) High-resolution CT of the chest showing mediastinal lymph node enlargement

PVOD/PCH was grouped in a subgroup of group 1 in the recent classification of PH (group 1′) (Table 33.1). Indeed, a clinicopathologic study analyzing specimens from 35 patients diagnosed as having either PVOD or PCH [8]. The authors 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. It has been hypothesized that capillary hemangiomatosis may result from an angioproliferative process associated with venous obstruction, as observed in PVOD.

Recently, genetic analysis confirm that the terms "PVOD" and "PCH" described the same entity indeed, we identified that bi-allelic mutations in *EIF2AK4* gene in the major genetic risk factor for PVOD/PCH [7]. *EIF2AK4* bi-allelic mutations was identified in 100 % of familial form of PVOD/PCH (n = 13 families) and 25 % of sporadic PVOD/PCH (5 of 20 histologically confirmed sporadic PVOD). Heritable PVOD/PCH is an autosomal recessive disease, characterised 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].

Moreover, we reported a higher tobacco exposure and an increased proportion of smokers in PVOD/PCH as compared to PAH [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 granulomatosis, a pulmonary disease occurring almost exclusively in smokers. Of note, cases of PVOD/PCH are diagnosed in the context of treatment with a number of chemotherapeutic regimens, notably alkylating agents. 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. 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. Pathological confirmation is usually obtained from autopsy or lung explants, and treatment decisions are usually based on clinicoradiological grounds. Distinguishing PVOD/PCH from PAH on clinical grounds alone is difficult since physical findings are often identical. Digital clubbing and Raynaud's phenomenon have been associated with PVOD/PCH but are observed no more frequently than in idiopathic PAH [5]. Auscultatory crackles may be indicative of acute pulmonary edema, occurring particularly after initiation of PAH specific therapy. In PVOD/PCH, measured values of the pulmonary capillary wedge pressure are characteristically in the normal range despite the involvement pulmonary venules. In the context of PVOD/PCH, the term "pulmonary capillary wedge pressure" is misleading since 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 capillary wedge pressure measured in PVOD/PCH do not represent a true reflection of the true capillary pressure [5, 6]. As a result, PVOD/PCH is characterized by a pattern of precapillary PAH on right heart catheterisation 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 [88]. 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 [91].

A non-invasive approach has been proposed to screen PH patients with a high clinical suspicion of PVOD/PCH [6]. These include high-resolution computed tomography of the chest, arterial blood gases, DLCO and more rarely bronchoalveolar lavage [4, 6]. 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 [92] (Fig. 33.4). Indeed, PVOD/PCH patients are characterised by significantly lower resting partial pressure of arterial oxygen and DLCO compared to those with idiopathic PAH [5, 89]. Finally, using bronchoalveolar lavage, Rabiller et al. showed that PVOD/PCH patients have significantly increased numbers of haemosiderin-laden macrophages and higher average Golde score (usually <100) [93].

The response to medical therapy and prognosis of PVOD/PCH are poor. An important clinical hallmark of PVOD/PCH is that patients may experience potentially life-threatening deterioration due to severe pulmonary edema after initiation of specific PAH therapy [5, 6, 94], 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 [6]. Nevertheless, because of the overall poor response to specific PAH therapy and poor outcomes, lung transplantation remains the treatment of choice of PVOD/PCH.

Conclusion

In conclusion, PH is associated with several orphan lung diseases, including sarcoidosis, Langherhans' cells histiocytosis, neurofibromatosis, lymphangioleyomyomatosis and combined pulmonary fibrosis and emphysema syndrome. As observed in end-stage chronic lung diseases, PH may be related to hypoxia and in proportion to the severity of parenchymal involvement. However, in these conditions, specific pulmonary vascular involvement associated with severe "out-of-proportion" precapillary PH may be reported, usually associated with a poor prognosis. PVOD/PCH represents a rare pulmonary vascular disease, sharing similarities with idiopathic PAH, but with important differences in diagnosis, management and outcome.

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34 Rare and Emergent Drug-Induced and Iatrogenic Respiratory Conditions: A Guide to Their Recognition and Management

Philippe Bonniaud and Philippe Camus

Introduction

Drug-induced and iatrogenic respiratory disease (DIRD) is a common diagnostic consideration in adults and children who present with new respiratory signs, symptoms or abnormal imaging or gas exchange [1]. Many DIRD are as rare as orphan conditions, and as such they run the risk of being underdiagnosed and underreported. Failure to recognize DIRD may result in delayed diagnosis, unnecessary investigation or treatment, extra-time on the medication and further irreversible harm to the patient's respiratory system. The group of interstitial/infiltrative lung disease (commonly abbreviated 'ILD') is the most common form of drug-induced (DI) respiratory involvement, accounting for about two thirds of all DIRD cases. Interstitial lung disease is subsumed into several subtypes including among others NSIP-like or cellular ILD, organizing and eosinophilic pneumonia and pulmonary fibrosis. The preponderance of ILD must not overshadow less common yet potentially life-threatening iatrogenic though curable patterns such as upper airway angioedema and obstruction, serositis, pulmonary vasculitis, involvement of the mediastinum, respiratory muscles/nerves, central respiratory oscillator or hemoglobin.

With 954 offenders, about 200 possible patterns of involvement and 21,400 bibliographic references, summarizing DIRD is challenging. To that end, the Pneumotox website was constructed to provide health professionals with comprehensive and updated information on respiratory conditions induced by drugs, abused substances, gases, chemicals and procedures [2, 3]. Pneumotox can provide information quickly, an important feature as drugs may cause life-threatening adverse effects of rapid onset, leaving a limited time frame to identify the reaction and act before irreversible respiratory failure has developed (Table 34.1). Avoidance of drug casualties is the *leitmotiv* of the website and of the present piece.

Drug-induced adverse reactions occur unexpectedly in a few individuals who are predisposed often without a clear reason for it, who receive the drug at normal dosage. There are usually little or no annunciating symptoms. Strictly speaking, drug overdosing is outside the province of drug-induced adverse effects, although overdoses of drugs can cause pulmonary edema, acute respiratory failure, the adult respiratory distress syndrome (ARDS), diffuse alveolar hemorrhage (DAH) and death. In addition, the limit between normal and above-normal dosage is blurred for such drugs as oral anticoagulants, thrombolytic agents, amiodarone, cyclophosphamide, bleomycin, nitrosoureas, salicylate and drugs of abuse, and for practical reasons respiratory injury associated with drug overdose will be covered here inasmuch as aging, impaired hepatic or renal function, drug interactions and/or variability in drug metabolism and clearance may alter drug disposition. Drug abuse and misuse (e.g. intravenous injection of crushed tablets intended for oral use) and chemical-induced respiratory injury are also covered here and in Pneumotox. Other complications from drugs include drug withdrawal-induced flare of the underlying condition, as shown by relapse of amiodarone pulmonary toxicity (APT) upon corticosteroids withdrawal, rebound respiratory failure following naloxone reversal of opioid intoxication [4], rebound pulmonary hypertension (PHT) following inadvertent cessation of pulmonary vasodilator therapy [5], or the recently-described ruxolitinib withdrawal syndrome [6].

Reports on drug-induced respiratory disease (DIRD) appeared as early as the late nineteenth century. The topic grew in the 1950s–1970s, and in 1973 about 120 drugs were known to injure the respiratory system [7]. This figure was propelled since the 1990s to 950 iatrogenic offenders at large, 15 main and 200 subpatterns. Classic offenders such as angiotensin-converting enzyme inhibitors (ACEI), amiodarone, anticoagulants, beta-blockers, bleomycin, cyclophosphamide, nitrosoureas and other chemo agents,

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Table 34.1 Life-threatening drug-induced/iatrogenic acute 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	ß-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 up to (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/ARF/ARDS
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	Doxurubicin, fluorouracil	Pulmonary edema
Multiple organ dysfunction syndrome	w-mo	d	Drugs that induce DRESS	Multi-organ dysfunction/ failure

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 antiinflammatory drug, *NSIP* nonspecific interstitial pneumonia, *PTU* propythiouracil, *RCM* radiocontrast media, *RILI* radiation-induced lung injury, *RVF* right ventricular failure, *TKI* tyrosine kinase inhibitor, *UAO* acute airway obstruction, *y* years, *h* hours, *d* days, *w* weeks, *mo* months, *min* minutes, *sec* seconds

[a]Complete list of offenders see pneumotox.com

blood transfusions, ergots, irradiation, methotrexate, minocycline, nitrofurantoin, nonsteroidal antiinflammatory drugs (NSAIDs) and salicylate still cause a persistent background of DIRD, although the current literature may not reflect it well as these adverse effects get rarely published nowadays. Drug-induced respiratory disease has garnered further interest as amiodarone, and novel biologicals and targeted agents such as tyrosine (TKI) or proteine kinase inhibitors (e.g. BCR-ABL), TNF-alpha antagonists, anti-CD20 (rituximab), inhibitors of the mTOR pathway, of platelet glycoprotein IIB/IIIA receptors, and direct antithrombin anticoagulants and reverse transcriptase inhibitors are now available to treat coronary artery disease, solid and hematologic malignancies, rheumatoid arthritis and other connective tissue disease (CTD), and systemic vasculitis. Targeted agents may cause on- and off-target adverse effects including but not limited to opportunistic infections [8, 9]. Exposure to these agents has been temporally related to the development of ILD, rapidly-progressive ILD, organizing pneumonia, eosinophilic pneumonia, sarcoidosis-like condition, diffuse alveolar hemorrhage (DAH), hypersensitivity, and anaphylaxis. Drugs, abused drugs, biologicals and silicone may also cause autoimmunity or autoimmune conditions [10, 11] with possible lung or serosal involvement including but not limited to *lupus erythematosus*, ANCA-related granulomatosis and polyangiitis (formerly known as Wegener's), PR3- or MPO-antineutrophil cytoplamsic antibody (ANCA)-related vasculitis [12], eosinophilic vasculitis (Churg-Strauss'), Goodpasture-like pneumorenal syndrome, inflammatory myopathy and the anti-phospholipid syndrome. Drug-induced systemic conditions may manifest in the chest exactly as they do when they occur idiopathically in the form of ILD, DAH, eosinophilic pneumonia, lung nodules, lymphadenopathy, pleuropericardial effusion, systemic myositis or pulmonary thromboembolism. Biologicals used to treat rheumatoid arthritis also interfere with TNF signaling pathway causing opportunistic pulmonary or and/or systemic infections including reactivation of latent tuberculosis infection (LTBI) [13].

The possibility of exposure to illicit drugs should also be raised in patients presenting with acute pulmonary edema, diffuse alveolar hemorrhage, upper airway injury/burns, ILD, acute eosinophilic pneumonia, organizing pneumonia, pulmonary granulomatosis, foreign body reaction, talcosis, acute bronchospasm, pneumothorax, pneumomediastinum, pulmonary hypertension, pleuritic chest pain and blackened material in the alveolar lavage fluid [14, 15]. History taking of exposure to abused drugs often is challenging.

Epidemiology

Amiodarone, methotrexate-, nitrofurantoin-, chemotherapy agents and radiation cause lung injury with a significant incidence rate (nitrofurantoin: 0.2 %; amiodarone 2–4 % per year). Incidence with most other drugs is low to very low, fitting the numerical definition for orphan diseases of <1/2,000 patients affected. The base of evidence for drug causality is heterogenous as many reports date back several years and few specific tests were or are available. In a few phase I or II combination chemotherapy regimens where bleomycin, CCNU, gemcitabine, or dasatinib were given concomitantly with irradiation, the incidence of DIRD could be as high as 50 % or more [16].

Drugs are a significant contributor for pulmonary diseases accounting for 3–5 % of all ILD cases [17], 10 % of ARDS [18], 11–18 % of DAH [19] or eosinophilic pneumonia and 30 % of organizing pneumonia cases. Four percent of all DIRD are fatal and about 8 % are preventable although risk evaluation and prevention are still in their infancy.

Drugs cause DIRD after variable times on the medication, from a few seconds for flash pulmonary edema [20], catastrophic bronchospasm or anaphylaxis [21], to months or years into treatment for many ILD, or even after termination of treatment for iatrogenic fibrotic conditions [22]. DIRD may develop regardless of route of administration of drugs, although the oral and parenteral routes are foremost. Drugs given *via* topical instillation (transdermal, ophtalmic, gingival, intra-uterine, endomyometrial, subcutaneously, or in the vertebral body, pleura, urinary bladder or intrathecally), *via* inhalation or aspiration may also cause substantial lung injury [2].

Clinically, DIRD may manifest with involvement of the lung, central or peripheral airways, pleural and/or pericardial surface, circulation, mediastinum, neuromuscular system, heart or hemoglobin [2]. Although drugs or drug families may cause stereotyped patterns of adverse effects (Table 34.2), drugs generally may cause more than one pattern of involvement depending on the patient, with amiodarone outdoing any other drug with over 20 possible patterns [2].

Illicit/abused drugs including alcohol (also harbored in Pneumotox) are relevant DIRD providers [2]. In the past 40 years, the death toll from opioids in the US increased ninefold, due to ventilatory depression, falls, and aspiration [23]. Subversion of drug use, herbals, dietary supplements, incense and chemical concoctions obtained through the Internet emerge as a cause of life-threatening respiratory disease [24, 25]. The new trend of 'Met-Labs' may cause life-threatening injuries to the manufacturer, family, law enforcement officers,

Table 34.2 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
			AEP	Can cause ARF. Good prognosis
Anticonvulsants	Carbamazepine, phenytoin, lamotrigine	****	**DRESS**	Rash, end-organ involvement, PIE in about 10 %
Anticoagulants (oral)	Coumadin, warfarin, brodifacoum	***	**Bland DAH**	Risk increases with the INR
	New direct anticoagulants (DOA)	**	**Laryngeal tongue hematoma**	May cause acute UAO
Anticoagulants and thrombolytic agents	Heparin, SK, UK, alteplase	**	**Bland DAH**	
			Hemothorax	Can cause tamponade and CV collapse
Antidepressants	Sertraline, venlafaxine		**AEP**	
			DRESS	
Antithyroid drugs	Propylthiouracil, benzylthiouracil	***	**Capillaritis, DAH**, systemic vasculitis	p- or c-ANCA present, often anti-HNE at high titers
				Renal involvement possible
Angiotensin receptor blockers	Sartans	**	**Angioedema**	Risk 1/10 1/20 compared to risk of ACEI
Beta agonists (parenteral tocolytics)	Salbutamol, terbutaline, isoxuprine	***	**NCPE**	Mostly in parturients. Fatal in 5 %
Beta-blockers	Most ß-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
Blood, blood products	Blood, blood components, FFP	****	TRALI	Onset in 6–8 h of transfusion
Curares	Pancuronium, tubocurarine	***	**Severe bronchospasm**	
		**	**Anaphylaxis**	
Cytotoxic agents	Bleomycin, busulfan, cyclophosphamide gemcitabine, nitrosoureas, taxanes	***	Transient pulmonary infiltrates	Caution as rechallenge may cause full-blown NCPE/ARDS
		****	**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
	Tacrolimus	*	'ILD'	Described almost exclusively in Japanese RA patients
	Biologics	****	ILD/SLE/DAH	See under TNF-alpha inhibitors
Ergots	Bromocriptine, cabergoline ergotamine, DHE, methysergide nicergoline, pergolide	****	Pleural effusion	
			Pleural thickening	
		***	Acquired valvular heart disease	Anorexigens produced similar valvular changes
Interferon alfa/beta		***	Cellular NSIP-like ILD	New drugs to treat viral hepatitis C infection may decrease the incidence
			OP	
			Sarcoid-like disease	
Leukotriene receptor antagonists	Montelukast, pranlukast, zafirlukast	**	Eosinophilic granulomatosis polyangiitis	Causal relationship needs 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 with reduction or discontinuance
			Rare PAP pattern	

(continued)

Table 34.2 (continued)

Drug or family		Incidence	Involvement	Comment
NSAIDs, aspirin	ASA, ibuprofen, indomethacin naproxen, piroxicam	****	**Severe bronchospasm**	Relapses on rechallenge
		**	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**	
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
	Mediastinum	**	**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

Abbreviations: *ACEI* angiotensin converting enzyme inhibitors, *AEP* acute eosinophilic pneumonia, *ANA* antinuclear antibody, *Ds-ANA* anti double strand antibody, *ANCA* antineutrophil cytoplasmic antibodyantibodies, *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, *ILD* interstitial lung disease, *INR* international normalized ratio, *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

firefighters and forensic personnel [26]. Other forms of DIRD include occupational asthma in pharmaceutical industry workers, and lung injury in pets and other animals, which closely resemble those seen in humans [27–29].

Diagnosis

To raise the possibility that a new respiratory problem is caused by the administration of a drug, a combination of drugs and/or radiation therapy can be important for the patient: further/irreversible damage can be prevented if use of the harmful drug is stopped (although the underlying illness needs be managed using other medications so that the patient is not exposed to a flare of the underlying disease), patients may be spared unnecessary invasive evaluation (e.g. a lung biopsy and/or empiric corticosteroid therapy) pending the result of a drug holiday which can be diagnostic, and unnecessary readministration of the causal drug can be avoided. A high index of suspicion for drugs or chemicals as the possible cause for any new respiratory problem is warranted regardless of age as DIRD can occur in children or in newborns, gender though a few DIRD are female- or male-specific or are unique to the pregnancy state and underlying condition. Altered sensorium and inability of the patient to communicate in the emergency setting may complexify history taking, which may then rest on relatives, family physician or pharmacist. A urine drug screen and blood levels of the suspect drug or chemical (e.g. paraquat, brodifacoum) are indicated as early as possible after admission, so as the compound has not cleared to insignificant levels [30]. Analysis of the time course of symptoms *vs.* exposure is indicated as both drugs and patterns differ in this respect. Literature should confirm that the observed pattern (symptoms, imaging, laboratory findings, BAL, pathology, outcome) is appropriate for the specific drug. Pneumotox was designed to expedite this search [2]. Diligent exclusion of other possible causes is required as drug-induced pneumonitis and infectious pneumonia may present similarly. The expanse of differential diagnosis varies according to drug, basic disease, clinical context, presentation, pattern of injury and whether the patient was being exposed to one or several drugs or immunosuppressive agents. Abatement or resolution of symptoms should follow drug discontinuance, preferably without adjunctive corticosteroid therapy otherwise drug dechallenge is more difficult to interpret. Hyperacute drug-induced cellular ILD, pulmonary edema, alveolar hemorrhage, ARDS and systemic reactions may not improve upon simple drug withdrawal and corticosteroid therapy is indicated in such case and can be life-saving. Absence of recurrence of symptoms within an appropriate observational period off the drug will support the drug etiology. Relapse after inadvertent or deliberate rechallenge with the drug is undisputable evidence for drug causality, but this test often is not available as rechallenge can be hazardous or cause patient's demise. Rechallenging the patient can be considered only if the drug is vital, there is no substitute for it, safe rechallenge has been described in the literature (e.g. imatinib, dasatinib, m-TOR inhibitors), and/or a prococol for rechallenge or induction of tolerance is available. Overall, 1.4 % of all DIRD cases have been rechallenged, leading to death of 7 % of those so managed. Lung pathology is rarely available in DIRD, being described in 3.8 % of all DIRD reports. Tissue abnormalities in drug-induced lung disease may be 'consistent with', 'suggestive of' or rarely 'diagnostic of' the drug etiology, which limits the contribution of this test. Table 34.3 lists the pathology patterns and whether BAL can be used as a surrogate test. The lung biopsy may have an important exclusionary role, whereby other illnesses or an infection can be ruled out with

Table 34.3 Drug-induced respiratory disease: pathology consistent with: pathology shows nonspecific findings and cannot support the diagnosis Suggestive: pathology shows distinctive findings that are distinctive enough to support the diagnosis specific: changes almost pathognomonic

Histopathologic pattern	Typical drug or drugs causing the pattern	Frequency	BAL surrogate?	Consistent with	Suggestive	Specific
Cellular ILD, NSIP-cellular-like	Methotrexate, nitrofurantoin, sirolimus	Common	Y if lymphocytic	X		
Eosinophilic pneumonia	Minocycline, NSAIDs	Common	Y		X	
Organizing pneumonia (OP pattern)	Amiodarone, interferon	Common		X		
Acute Fibrinous Organizing Pneumonia AFOP	Amiodarone	Uncommon				
ILD with a granulomatous component	BCG, interferon, methotrexate	Common		X		
ILD with a necrotizing granulomatous component	BCG, marijuana, methotrexate	Uncommon				
Diffuse alveolar damage DAD	Chemotherapy, irradiation	Common		X	X	

(continued)

Table 34.3 (continued)

Histopathologic pattern	Typical drug or drugs causing the pattern	Frequency	BAL surrogate?	Consistent with	Suggestive	Specific
A reactive epithelium, pneumocyte atypia	Alkylating chemotherapy, irradiation	Common	Y	X	X	
Diffuse alveolar hemorrhage DAH	Anticoagulants, platelet aggregation inhibitors	Quite common	Y	X		
Pulmonary fibrosis, NSIP-fibrotic	Chemotherapeutic drugs	Common				
Pleuroparenchymal fibroelastosis	Cyclophosphamide	Rare				
UIP pattern	Chemotherapeutic drugs	Common				
DIP pattern	Amiodarone, nitrofurantoin, sirolimus	Unusual		X		
GIP pattern	Nitrofurantoin	Rare		X		
LIP pattern. Lymphoid hyperplasia	Amiodarone	Unusual		X		
PAP pattern – secondary PAP	Busulfan, sirolimus	Rare	Y			
Endogenous lipoid pneumonia – phospholipidosis	Amiodarone	Very common	Y/N		X Changes in amiodarone pulmonary toxicity can be very suggestive	X Or nearly so
Exogenous lipoid pneumonia	Paraffin, mineral oil	Common	Y			X Lipid staining diagnostic
Interstitial foreign body granuloma	Abused drugs, talc	Uncommon	Y			X
Smudged parenchymal necrosis	Amiodarone	Uncommon			X	X
Pneumoconiosis, talcosis	Abused drugs, talc	Uncommon	Y			X
Amyloid deposits	Insulin	Rare				
Crystal storage disease	Clofazimine	Rare				
Diffuse pulmonary calcification	Calcium replacement	Rare		X		X
Bland pulmonary edema	Chemotherapy, salicylate	Common		X		
Subacute/acute cellular bronchiolitis	Aspirated food, tobacco smoke, talc	Uncommon			X	X (if demonstrable food particulate matters in tissue)
RB-ILD	Tobacco smoke	Common	Y?		X (if pigmented macrophages present)	
Constrictive obliterative bronchiolitis	?Penicillamine ?Gold. *Sauropus androgynus*	Rare				
Foreign body bronchiolitis	Talc	Uncommon	Y			X
Pulmonary capillaritis	ATRA, PTU	Rare		X		
Pulmonary vasculitis other than capillaritis	Hydralazine, tryptophan	Rare		X		
Eosinophilic vasculitis	Tryptophan	Uncommon	Y		X	
Fat/marrow embolism	Parenteral nutrition, propofol, vertebroplasty	Uncommon	Y		X	
Silicone embolism	Fluid silicone	Uncommon				X
Foreign body vasculopathy	Talc, excipients	Uncommon				X
Elemental mercury embolism	Liquid mercury	Rare				X
Cement embolism	Acrylate cement	Uncommon				X
Crystal pulmonary embolism	i.v. lipids	Rare			X	

Table 34.3 (continued)

Histopathologic pattern	Typical drug or drugs causing the pattern	Frequency	BAL surrogate?	Consistent with	Suggestive	Specific
Venoocclusive disease	Antineoplastic chemotherapy	Uncommon		X		
Pulmonary hypertension	Anorexigens	Quite common[a]		X		
Pleuritis	Radiation therapy, drug lupus	Common		X		
Eosinophilic pleuritis	Propylthiouracil PTU	Uncommon		X		
Pleural fibrosis	Amiodarone, ergots, drug-induced lupus	Common			X	
Fire eater's lung	Kerdane, petrolatum	Uncommon			X	
Kayexalate lung	Kayexalate	Uncommon				X
Alveolar carbonaceous deposits	Crack cocaine	Uncommon	Y			X

Where BAL can reasonably be used as a substitute or 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
Watching the progress of cryolung biopsy is indicated
Blank/void cell indicates absence of data
[a]Drug has been recalled

Table 34.4 Check list for diagnosing drug-induced respiratory disease

No evidence for pulmonary disease prior to therapy with the drug
Event unlikely in the course of the specific disease state
Confirmed exposure
Eligible drug
Drug singularity
Absence of prodromal signs and symptoms prior to exposure to the drug
Appropriate timing (latency time, onset) relative to taking the medication
Pattern appropriate for the drug under scrutiny
Confirmatory literature (qualitative: consistency, quantitative: magnitude)
Supportive imaging, laboratory, BAL, pathological features
Laboratory evidence including blood levels
Reasonable exclusion of other causes including an infection and the effects of other drugs
Abatement or resolution with discontinuation of drug, preferably without corticosteroid therapy
Lack of recurrence is patient not rechallenged
Relapse following rechallenge with the drug

greater certainty. The recently described cryobiopsy technique is being currently evaluated [31]. Diagnostic criteria are summarized on Table 34.4. Overall, only a few cases can be definitely ascribed to drugs, namely those with a distinctive pathology or positive rechallenge. In a fraction, drugs can be ruled out, and the vast majority is labled possible or probable, with all uncertainty left to such wording [32]. Classic papers by Hill [33] and the Naranjo scoring system [34] still are valuable resources. The topic of counterfeit drugs [35] and the recent issue of fake journals [36] is a further challenge in evaluation the materiality of DIRD; continued vigilance is necessary.

Rare Drug-Induced Respiratory Disease

The orphan patient is the one presenting with DIRD in whom the diagnosis is not raised and drug dechallenge is not attempted. A list of common inducers and the corresponding clinical-imaging-pathologic patterns of involvement is given in Table 34.5. Being supported by a wealthy and persistently fueled literature, involvement from these drugs is not reviewed here in great detail although atypical respiratory presentations from some of these compounds is reviewed later in this text.

Adverse Respiratory Reactions with Indeterminate Evidence for Causality

About half the 950 drugs and agents censored in Pneumotox at this time cause ILD with a low to very low incidence rate (<10 reports overall despite many years on the market), indicating circumstantial evidence for causality. Reports are heterogenous [37], often date back many years, details were not given, patients were managed empirically with drug withdrawal and corticosteroid therapy making retrospective assessment difficult. The issue of causation *vs.* chance association is an unresolved one at this time and may remain so in the foreseable future. These drugs appear in Pneumotox with a 0–1 frequency [2].

Drugs Recalled or Fallen Out of Favor

Mecamylamine, hexamethonium, aminorex, tryptophan, fenfluramine, dex fenfluramine and benfluorex have all been recalled. We keep them in Pneumotox though, as any drug

Table 34.5 Drug-induced respiratory disease: common inducers and patterns of involvement

	Typical clinical imaging pattern	Incidence/RR	Practical risk factors	Clinical presentation	Onset	Management	Comment
ACEI	Cough	RR 2.5	Varies with ACEI	Chronic dry cough	w-y	DW	Resolves in all
	Angioedema	0.1–0.4 % – RR 7.7	Dark-skinned people	Acute UAO/Asphyxia	w-y	DW	Fatal in 5 %
Amiodarone	ILD, endogenous lipid PNA	Up to 4 %	Dosage, time on drug, O2	Dyspnea, cough	d-y	Corticosteroids	Can leave residual fibrosis
Anticoagulants, oral	DAH. Airway hematoma	Rare	INR-dependent	Acute dyspnea & anemia	w-y	DW vitK FFP	BAL diagnostic
Anticonvulsants	DRESS syndrome	Up to 1/1,000	Familial incidence	Skin, deep-seated involvement	mo-y	DW	Mortality ca. 5 %
Aspirin/salicylate	Pulmonary edema	45 % of those poisoned	Elderly	NCPE, M metabolic acidosis	h-mo	DW, alkalinization dialysis	Mortality up to 15 %
ATRA	Pulmonary edema, DAH	6–27 %. Less if CS given	Leukocytosis	Pulmonary edema ARDS DAH	d	Supportive + corticosteroids	Mortality up to 13 %
Beta-blockers	Bronchospasm	Common	Asthma, atopy	Acute bronchospasm	min	Supportive + DW	25 % fatal
Bleomycin	Pulm infiltrates ARDS	About 10 %, up to 22 %	Retreatment, age, smoking, dose, O2	Basilar/diffuse infiltrates	w-mo	Supportive + DW + steroids	Up to 24 %
Chemo agents	Pulm infiltrates ARDS	Usually about 5 %	Dose, oxygen, ? CSF	Basilar/diffuse infiltrates	w-y	DW + corticosteroids	Fatality in DAD
Cyclophosphamide	Pulm infiltrates ARDS fibrosis	Up to 12 %	Dose, oxygen	Basilar/diffuse infiltrates	w-y	DW + corticosteroids	Up to 40 % mortality
Drugs of abuse	Pulm infiltrates, ARDS, EoP	Difficult to evaluate	Dose	Infiltrates pneumothorax burns	min-y	DW (corticosteroids)	Panoply of AEs
	PHTn		Injection of crushed tablets	PHTn	y	Treat PHT, consider Tx	UDS indicated
Ergolines	Pleural thickening	Unknown	None identified	Restrictive lung dysfunction	y	DW corticosteroids rarely indicated	No fatalities. May leave residual
Gemcitabile	Pulmonary infiltrates NCPE	0.03–2 %	Concomitant bleomycin or irradiation	NCPE, ARDS	Within 2 mo	DW corticosteroid therapy	Mortality 20 %
	HUS	2.2 %		NCPE, DAH, renal failure			
Gold	Acute NSIP	Unknown	None identified	Diffuse infiltrates	w-y	DW + corticosteroids	Drug out of favor
Lipid (p.o.)	Exogenous lipoid pneumonia	15 % of institutionalized patients	Chronic aspiration	Basilar infiltrates	mo-y	DW. Corticosteroids ?	A disease of the elderly or with achalasia
Methotrexate	Acute NSIP	0.9–3 %	? previously diagnosed ILD	Diffuse infiltrates	w-y	DW. Corticosteroids	Common in RA
Minocycline	Acute eosinophilic pneumonia	Unknown	? Atopy	Peripheral or diffuse infiltrates	w-mo	DW. Corticosteroids	Distinctive pattern
	Autoimmune ANA/ ANCA disease	Unknown		Pleuropulmonary reaction		DW. Steroids. IS. Plasma exchange	When assayed ANA in 45 %; ANCA in 7 %
							Some patients developed PAN

m-TOR inhibitors	Pulmonary infiltrates	Up to 35 %	Somewhat dose-related	Basilar pulmonary infiltrates. DAH	w-mo	Dose reduction. DW. Corticosteroids	Fatal cases among DAH ILD may equate efficacy in RCC Diagnostic challenge in lung Tx recipient
Nitrofurantoin	Acute pleuropulmonary reaction	1/5,000	None indentified	Acute dyspnea + chest pain	d-w	DW. Corticosteroids	Some patients have ANA
	Chronic ILD or fibrosis	1/15,000–45,000	None indentified	Chronic dyspnea	mo-y	DW. Corticosteroids	
NSAIDs	Asthma, anaphylaxis	Clinical: 3 %	Atopy	Acute bronchospasm	min	O2, corticosteroids, MV	Cross reaction among COX1 inhibitor drugs
	Eosinophilic pneumonia	Higher on airway challenge	None identified	Bilateral infiltrates	mo	DW. Corticosteroids	Induction of tolerance possible
Nitrosoureas	Acute lung injury, ARDS	3–5 % overall	Dose, young age	Basilar or diffuse infiltrates	w-mo	DW. Corticosteroids	A fraction will respond to steroids
	Pulmonary fibrosis			Basilar or diffuse infiltrates	mo	DW. Corticosteroids	Can be devastating
Phenytoin	DRESS syndrome	1/1,000–1/10,000	Family history	Multiorgan	W	DW ?Corticosteroids	Other anticonvulsants may cross-react
Radiocontrast media	Anaphylaxis	02/100.000 PY – 1.2/ million doses	Atopy	CV collapse, arrest, angioedema, shock	min	Withdrawal	
Sulfasalazine	Eosinophilic pneumonia			Basilar or diffuse infiltrates and eosinophilia	mo	DW. Corticosteroids	Needs be separated from effect of IBD on lung
TKI	DAD-ARDS	1–5 % in Japan 0.3 % outside Japan	Prior ILD	Basilar or diffuse infiltrates	d-w	DW. Corticosteroids	Fatality rate up to 40 %

C condition, *CSF* colony-stimulating factors, *DRESS* the syndrome of drug rash, eosinophilia and systemic symptoms, *DW* drug withdrawal or dechallenge test, *HUS* hemolytic and uremic syndrome, *LVDF* left ventricular dysfunction or failur, *PAN polyarteritis nodosa, RCC* renal cell carcinoma, *RR* risk ratio of developing the condition *vs.* untreated subjects (when data available), *TKI* tyrosine kinase inhibitors, *y* years, *h* hours, *d* days, *w* weeks, *mo* months, *min* minutes

may regain popularity in light of a new indication as is the case with thalidomide, or because related congeners may reproduce DIRD similar to those of the parent compound.

The antneoplastic antibiotic mitomycin-C is now less commonly used than it once was. Mitomycin pneumonitis developed in about 5–10 % of the patients in the form of acute lung injury and DAD followed, in some patients by irreversible pulmonary fibrosis [38]. Corticosteroids have been effective in reversing early cases [39]. Mitomycin-associated hemolytic uremic syndrome is a rare (incidence 0.015 %) dreadful dose-related complication of mitomycin, gemcitabine and other chemotherapy regimens [40–42]. The syndrome is characterized by any association of hemolytic anemia, circulating schizocytes, thrombocytopenia, reticulocytosis, hyper- or hypotension, renal failure central nervous system symptoms, renal failure, pulmonary edema, alveolar hemorrhage, ARDS and/or pulmonary hypertension. Blood transfusions can trigger the onset of or aggravate the syndrome. Pathologic appearance is with intravascular pulmonary fibrin thrombi, pulmonary edema, hemorrhage and/or DAD. Management includes plasmapheresis, renal replacement therapy and high-dose corticosteroids. Serial monitoring of renal function and urinalysis may indicate those patients with early impending toxicity [43].

The once popular antirheumatoid drugs gold and penicillamine have mostly fallen into disuse since the advent of methotrexate, leflunomide and TNF-alfa antagonists. Severe gold-induced NSIP-like disease, obliterative bronchiolitis and Goodpasture like disease from penicillamine are for now diseases of the past [2].

Amphetamine-like anorectics (aminorex in the 1960s, fenfluramine-dexfenfluramine in the 1990s, benfluorex in the 2000s,) were recalled on the basis of acquired pulmonary hypertension (PHT) or valvular heart disease. As early as 1977, Widgren et al. reported on plexiform arterial lesions in the pulmonary circulation of young ladies who had used the anorectic aminorex [44]. In the series by Gurtner [45] prior to the advent of new therapies for PHT, death was mainly from right ventricular failure after an average of 3.5 years. Patients with higher grades of pulmonary artery pressures had worse outcomes. However, the prognosis was not as severe as that of primary PHT. Pathologically, aminorex vasculopathy is similar to primary PHT and similar findings have been reported with the use of other anorexigens [46, 47]. The aminorex epidemic peaked in the 1960s and declined in the early 1970s concomitant with aminorex discontinuation. Although household manufacture of aminorex has been responsible for sporadic PHT cases [48], most of the concern with aminorex now resides in its precursor levamisole, a veterinary anti-helminthic agent that is widely used since the early 2000s to cut street cocaine [49]. Levamisole is bioconverted to aminorex in mammals [50]. One PHT case has been documented following cocaine-levamisole abuse [51], and the topic is closely monitored. Accordingly, history of exposure to cocaine and other PHT inducers is indicated in any PHT case [52]. On the other hand, levamisole can produce a distinctive p-ANCA (with dual anti-PR3 and -MPO specificity) cutaneous vasculopathy mainly involving the face, earlobes and limbs, which is covered in more detail below [12].

The potent 5-HT2B receptor antagonist anorexigen fenfluramine and its dextro-isomer dexfenfluramine have also caused a PHT epidemic with a 6.3-fold increase in risk compared to nonusers [53]. Current data from the UK and Ireland Registry indicates a 1.7 % prevalence of antecedent anorexigen use among PHT cases [54]. In addition, fenfluramine caused valvular heart disease in the form of mainly left-sided valvular retraction with regurgitation or stenosis [55]. Fenfluramine and its dextro-isomer were recalled for that reason in the late 1990s. Benfluorex was promoted as an antidiabetic drug while in fact this is a fenfluramine prodrug. Vast numbers of valvular heart disease [56] and a few PHT cases developed in France following longterm indiscriminate exposure to the drug [57]. The drug was recalled in 2009.

Illicit amphetamines remain of concern as regards ‘primary’ PHT. An undeniably strong association between stimulant use (amphetamine, methamphetamine, cocaine) and ‘idiopathic’ PHT cases has been noted in western USA [58]. Chin et al. found a history of stimulant use in 28.9 % of their ‘idiopathic’ pulmonary hypertension cases, ten-fold that in nonidiopathic PHT [58].

Several members of the thiazolinedione (glitazones) family were discontinued in some countries owing to their propensity to cause capillary leak, pleural effusions and at times irreversible heart failure [2].

L-tryptophan once was a popular neutraceutical. The compound has produced an epidemic of ‘eosinophilia-myalgia syndrome’ [59]. Blood eosinophils were increased, about half of affected patients presented with small irregular or dense radiographic opacities and pleural effusion. An ARDS picture was noted in a few [2]. Minute amounts of contaminants (denoted peak and a suffix) formed during the bioengineered-driven synthesis of tryptophan at the Showa Denko plant were blamed as the cause for the syndrome. Incident cases diminished sharply after l-tryptophan was recalled. Only rare sporadic cases are now being reported [60].

Potentially Life-Threatening Emergencies

Pulmonologists, anesthesiologists, emergency physicians, intensive care and ENT specialists, dental and other surgeons can be confronted with acute life-threatening drug-induced respiratory and/or systemic emergencies. These reactions can affect (by decreasing order of frequency) the lung, upper or lower airways, pulmonary circulation, pleura or they are systemic in nature with pulmonary involvement in association.

Clinical presentations are in the form of diffuse white-out of the lung corresponding to several forms or acute lung injury or airway emergencies. The causal relationship with administration of a drug is deduced from the brief time-to-onset of the reaction upon exposure, which can be of seconds. Some reactions develop electively during the intra- or perioperative period, causing difficult diagnostic and management issues. Recognition of the drug etiology is paramount and can be life-saving.

White-Out and the Adult Respiratory Distress Syndrome (Table 34.6 and Fig. 34.1)

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 arterial oxygen to FIO2 of less than 300 [61]. Although this classification is relevant to the stratification of disturbances in gas exchange, it does not reflect lung pathology well. Notwithstanding the common lack of tissue available for review, the lesional pattern-based classification used by pathologists is appropriate to disentangle the group of ARDS as defined clinically and on gas exchange and has practical implications as regards the recognition, understanding and assessment of drug causality and patients' management. Pathologically, the majority of ARDS cases show the features of diffuse alveolar damage (DAD) [62, 63]. A smaller proportion corresponds to pulmonary edema, acute- NSIP or granulomatous ILD, -eosinophilic pneumonia (AEP), organizing (OP) or -fibrinous organizing pneumonia (AFOP), or diffuse alveolar hemorrhage (DAH) with or without circulating autoantibodies (ANCA, ANA) (Table 34.6). Although pathologically distinctive, the above patterns are rarely specific for the drug etiology (Table 34.3). Diagnosis is best approached noninvasively using literature holdings, imaging features, BAL, exclusion of another cause particularly an infection and response to drug therapy withdrawal and corticosteroid therapy. Imaging is a relevant adjunct for diagnosing drug-induced lung disease and separating it from other conditions to which DILD may resemble [15, 64–74]. The chest radiograph is examined as regards vascularity, septal lines, the vascular pedicle, heart, fissures, haze, and pleural/pericardial effusion [75]. Features of interest on HRCT include haze, ground-glass, inter- or intra-lobular septal thickening, crazy-paving, pleural effusion, zonal consolidation, micronodules, lymphadenopathy, increased attenuation of lung and liver tissue, and parenchymal calcification. Data in Table 34.6 may help establish a likely diagnosis for ARDS and from this analysis, to deduce an appropriate management strategy.

Acute pulmonary edema (Fig. 34.2) can develop quickly following inadvertent or deliberate overdoses of drugs or chemicals [2] including carbamates, calcium channel blockers (nicardipine, nifedipine, verapamil), tricyclic antidepressants, abused drugs including heroin, cocaine, amphetamine and salicylate [66, 76–82]. The naloxone test and urine drug screen may be indicated in patients suspect of being overdosed with opiates. Monitoring of blood levels should be ordered in salicylate intoxicated patients since dialysis may be indicated in severely poisoned acidotic patients with salicylate levels above 100 mg/dL [30]. Drug-induced pulmonary edema (DIPE) is defined by the subacute-to-rapid onset of pulmonary infiltrates coexisting with hypoxemia and a normal cardiac function, heart ultrasound and pulmonary capillary wedge pressure if measured, in a patient receiving one of the 171 compatible drugs taken at normal dosages in the absence of other explanation. DIPE may develop following oral, parenteral or topical administration of such drugs as epinephrine, treninoin (ATRA), arsenic trioxide (As203), salicylate, CSF, hydrochlorothiazide, nafazoline, opiates, propofol (a drug with potential for addiction) [83], i.v. ß2 agonists when used as tocolytic agents near term, the chemo agents gemcitabine, methotrexate, mitomycin C or taxanes, and radiocontrast agents. Pulmonary edema can also be a complication of drug-induced anaphylaxis. Hydrochlorothiazide- and salicylate-induced pulmonary edema is diagnosed suboptimally [30, 84, 85]. The edema may develop with intake of as little as one tablet of the causal drug and the diagnosis is sometimes raised by patient or family. Abrupt onset in minutes or a few hours following exposure and rapid clearing in a few hours or days upon drug stoppage are characteristic features of DIPE. In one case, pulmonary edema developed as a consequence of radiocontrast material (RCM) administration during HRCT examination, lobular pulmonary shadowing and septal lines denoting edema were noted 25 s following drug administration [20]. Such episodes are labeled 'flash pulmonary edema' to reflect the extreme shortness of onset [86]. Some DIPE cases may evolve to full-blown ARDS picture after stepwise increases in edema severity with each administration of the causal drug. Severe pulmonary edema classically but exclusively so in drug abusers may be heralded by a plume of protein-rich frothy sputum at the mouth (with a protein to plasma fluid ratio >0.7) [87]. Fever, hypotension, shock and hemoconcentration concomitant with the appearance of pulmonary infiltrates characterize hydrochlorothiazide-induced pulmonary edema [88]. Instances of pulmonary infiltrates waning in a few hours have been noted after exposure to crack cocaine, hydrochlorothiazide, nitrofurantoin and antithymocyte globulin [2] may also correspond to drug-induced pulmonary edema for lack of better fit, although pathology is rarely available.

Imaging studies in DIPE disclose diffuse haze, ground-glass and septal thickening. Sometimes pleural fluid is present [66]. Typical cases show no enlargement of the heart or vascular pedicle on frontal chest radiographs, except if circulatory

Table 34.6 Acute life-threatening reactions potentially causing ARDS

Clinical pathological diagnosis	Subpattern	Pathology	Typical drugs/agents	Time to onset	Tempo	BAL	Imaging (may predominate in LL)	Diagnosis	N drugs
1. Pulmonary edema	Pulmonary edema	Pulmonary edema & alveolar flooding	Chemo, ARA-C, HCT, ß2+	Short	Acute		GGO + pleural effusion	Normal heart, short tempo	170
	Flash PE	?Pulmonary edema ?DAD	Adrenaline, RCM	Ultrashort <5 min	Hyperacute		Haze, GGO, lobular thickening	Tempo, foam at mouth	9
	Transient pulmonary infiltrates	Pulmonary edema, DAD, vaculitis	Paclitaxel, ATG	Short	Acute		Slight haze, GGO, lobular thickening	Short-lived; relapse on rechalleng	6
	Pulmonary edema & shock	Pulmonary edema	Hydrochlorothiazide	Short	Acute-to-hyperacute	N	Alveolar shad ± pleural eff.	Tempo, shock, relapse on rechallenge	2
	Salicylate pulmonary edema	Pulmonary edema, DAD	Salicylate	Variable	Subacute	N	Alveolar shadowing ± pleural eff.	Salicylemia, metabolic acidosis, anion gap	1
	TRALI	Pulmonary edema, DAD, DAH	Blood, blood componenta, plasma	Within 8 h	Acute	N	Bilateral infiltrates or whiteout	Tempo – Relevant antibody in donor	6
2. Acute ILD	Chemotherapy lung	Pulmonary edema, NSIP, DAD, reactive pneumocytes	Chemo agents	Days-Weeks	Acute/ Subacute	N + reactive cella	Haze, GGO, consolidation, whiteout		50
	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	81
	Acute granulomtous ILD	Acute granulomatous ILD	BCG, fludarabine, IFN, MTX	Variable	Acute	L	Bilateral infiltrates	Pathology	24
	Acute foreign body reaction	Foreign body granuloma	Talc, crospovidone, food	Subacute	Subacute	–	Bilateral infiltrates	BAL, pathology	9
	Acute eosinophilic pneumonia	AEP	Minocycline	Weeks	Acute	E	Bilateral infiltrates	Eos blood/BAL	28
	Acute OP/AFOP	OP/AFOP w/wo foam cells	Amiodarone, statins	Variable	Acute	M	Bilateral infiltrates	Pathology	7
	Accelerated pulmonary fibrosis	Dense interstitial fibrosis	Bleomycin, nitrosoureas, anti-TNF, paraquat	Days to weeks	Subacute	N	Bilateral infiltrates	Pathology	17
	Acute amiodarone lung	NSIP w/wo a DIP pattern	Amiodarone	Weeks-months	Acute	M	Bilateral infiltrates	BAL/Pathology	1
	Acute postoperative APT	DAD + foam cells	Amiodarone	Acute	Acute	M	Bilateral infiltrates	BAL/Pathology	1

3. DAH	Bland DAH	DAH	All anticoagulants, antiplatelet	Variable	Acute	RBC	Bilateral infiltrates	BAL	102
	ANA-related DAH	DAH	Hydralazine, PTU, anti TNF	Variable	Acute	RBC	Bilateral infiltrates	BAL + Ab	3
	ANCA-related	DAH w/wo capillaritis	PTU, cocaine levamisole	Variable	Acute	RBC	Bilateral infiltrates	BAL + Ab	7
	Secondary DAH	DAH and silicone or hyaluronate	Silicone, hyaluronate	Short	Subacute	RBC	Bilateral infiltrates	BAL, silicone, hyaluronate	2
4. Exacerbation of preexisting IPF	Subacute	NSIP/OP + fibrosis	Any drug causing ILD	Variable	Acute	L/E/N	Aggravated bilateral infiltrates	?BAL	Many
	Precipitous	DAD + PF	Amiodarone, anti TNF, chemo	Variable	Acute	N	Bilateral infiltrates	-	24
5. Acute vasculopathy	Fat embolism syndrome	Fat embolism	Amphotericin, propofol	Short	Acute	AM[a]	Bilateral infiltrates	BAL	10
	Silicone embolism sd	Silicone embolism	Subcutaneous silicone injections	Hrs-days	Subacute/ Acute	AM[a]	Bilateral infiltrates	BAL/Pathology	1
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 inclusions

overload and/or left ventricular failure are present. Lobular septal thickening correlates with excess fluid in lung. On pathology or in autopsy cases, alveolar filling with acellular proteinaceous fluid or fibrin and moderate interstitial congestion are noted [2]. Hyaline membranes characterize those cases with overlapping features with DAD. Yet other DIPE cases overlap with DAH.

Salicylate-induced pulmonary edema can occur in both acute and chronic users, with a predilection for the elderly and in those with renal dysfunction [30]. Patients present with fever, systemic symptoms, neurologic symptoms including obtundation and anion-gap metabolic acidosis is suggestive. Thirty mg/dL is considered the threshold above which pulmonary and systemic toxicity is more likely to occur [30]. Management includes serum and urine alkalinization, with hemodialysis being reserved for cases with pulmonary edema, distant organ damage *and* >100 mg/dL blood levels [30].

Drugs including doxorubicin, epinephrine, fluorouracil, TKI and illicit drugs may cause myocardial infarction and/or acute left ventricular failure with consequent cardiac pulmonary edema [2].

Care should be taken so that patients with DIPE do not get reexposed to the causal drug, as severe relapse may ensue. Mortality in DIPE is significant (5–20 %).

The 'chemotherapy lung' may complicate therapy with many solo or multiagent antineoplastic drug regimens with an average incidence of 1–5 %. Elevated dosages of drugs, rapid i.v. as opposed to slow infusion, concomitant administration of bleomycin and gemcitabine, oxygen, rituximab, radiation therapy or CSF are triggering or aggravating factors. Drugs causing the syndrome include antibiotics (bleomycin, mitomycin C), alkylating agents (busulfan, chlorambucil, cyclophosphamide, melphalan), antimetabolites (azathioprine, cytosine arabinoside, gemcitabine, fludarabine, 6-mercaptopurine, methotrexate), etoposide, nitrosoureas, oxaliplatin, and taxanes [2, 18]. Recent additions include the TKI erlotinib, gefitinib, cetuximab, irinotecan and pemetrexed, although there is concern about which diagnostic criteria are used in the east. The condition manifests with cough, dyspnea, hypoxemia, diffuse haze or ground-glass that may progress rapidly to bilateral consolidation and loss of volume. HRCT imaging discloses inter- and/or intralobular

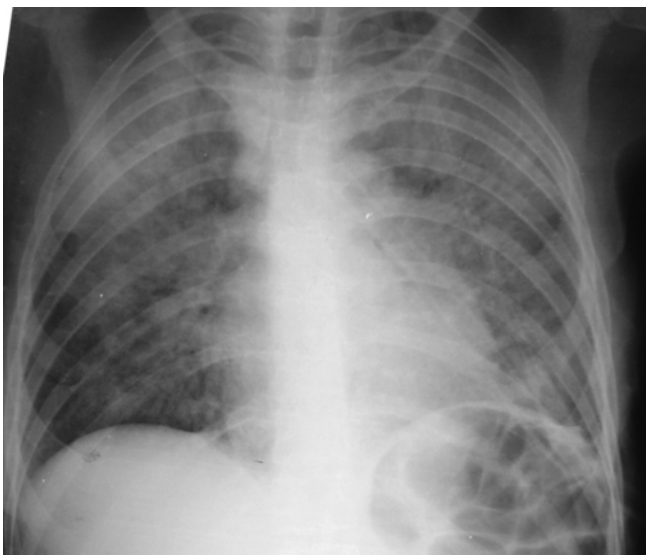

Fig. 34.1 Cellular ILD: methotrexate lung (chest tube present on lef post lung biopsy)

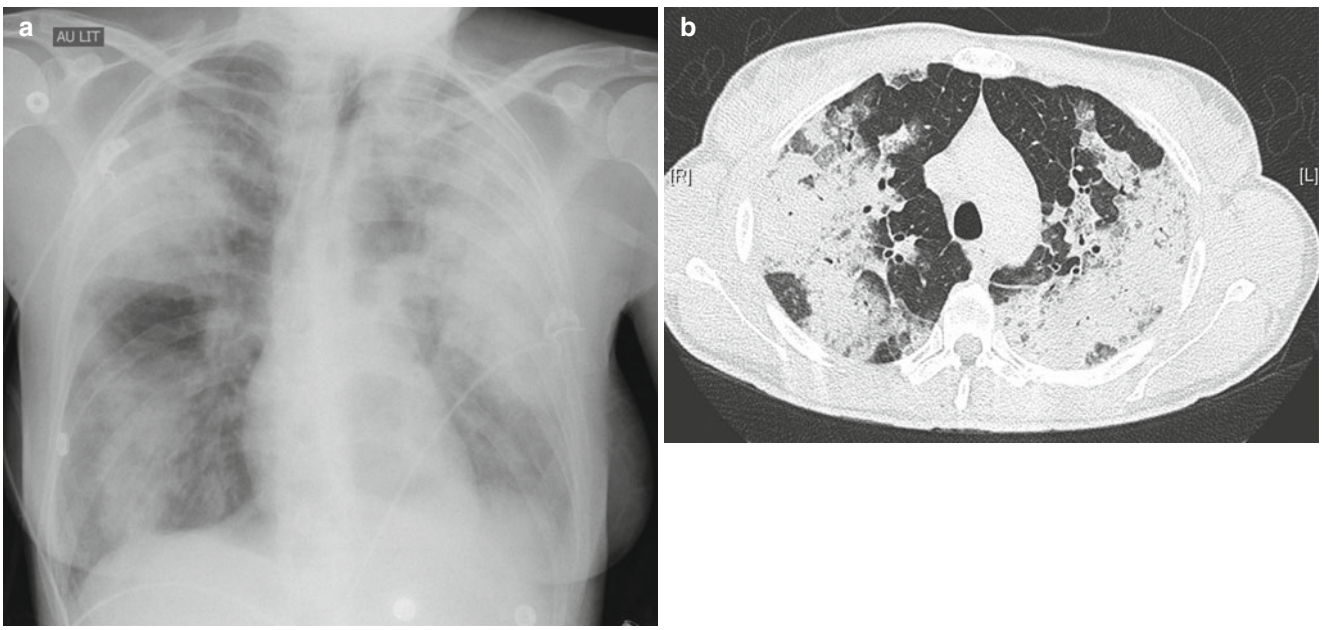

Fig. 34.2 (**a**) Eosinophilic pneumonia: presumed to be caused by a leukotriene receptor inhibitor drug. Corresponding CT scan on (**b**)

septal thickening, ground-glass attenuation and at times moderate bilateral pleural effusion is present. Patients on sequential chemotherapy, notably bleomycin need be monitored as they may develop subclinical lung restriction and progressive deterioration of CO diffusing capacity. Then, subclinical pulmonary infiltrates presumed to indicate early DAD may develop, with patients deteriorating in a stepwise manner on continued exposure to the drug to the full-blown chemotherapy lung or ARDS [89]. Caution is required in the asymptomatic patient when the diffusing capacity for CO falls by >40 % from baseline on serial measurements [90]. Unfortunately, several studies have questioned the validity of such follow-up which may not pick those patients who will ultimately develop the disease [90]. The BAL is generally performed in symptomatic patients suspect of having developed the chemotherapy lung to exclude pneumocystis or viral infection. There in an increase in neutrophils, hemosiderin-laden macrophages and bizarre type II cells in the BAL, the latter reflecting alkylating agent-induced cellular atypia which is particularly marked with busulfan [2]. A lung biopsy is rarely ordered, as the procedure has a certain attrition rate against a modest perceived diagnostic benefit. Depending on stage of the illness and because the lesions are not uniform throughout the lung, interstitial edema, alveolar fibrin, hyaline membranes, various stages of resolving or organizing alveolar damage, atypical alveolar lining cells, interstitial edema and fibrosis can be present [62, 91, 92]. Histopathological changes of DAD, to which ARDS typically correspond clinically, are also observed in the setting of infection, hematopoietic stem cell or solid organ transplantation, or concomitant with an exacerbation of preexisting pulmonary fibrosis [93–95]. DAD may also occur idiopathically in about 20 % of the cases. For practical reasons, drug-induced disease is considered likely when the workup for an infection is negative and there is a compatible drug history. Antibiotics and corticosteroids are given empirically, but the results of this form of therapy are unpredictable. About 40 % of early cases will respond to corticosteroid therapy, while more advanced cases may evolve to racalcitrant ARDS or progressive pulmonary fibrosis. Mortality of drug-induced chemotherapy lung can be as high as 45 %.

Transfusion-Related Acute Lung Injury

Acute noninfectious respiratory reactions following blood transfusion are subsumed into anaphylaxis, transfusion-associated circulatory overload (TACO) [96, 97] and transfusion-related acute lung injury (TRALI) [98]. All three entities carry a significant risk of severe respiratory failure. TACO has an incidence of 1–8 % and develops when the recipient's circulatory system is overwhelmed by the volume transfused or rate at which it is infused. Poor left ventricular reserve is a risk factor for TACO to develop. TACO manifests with hydrostatic pulmonary edema and it is often difficult to reliably separate the condition from TRALI purely on clinical and/or imaging grounds. The adjunctive role of transient elevation of blood NT-pro-BNP to differentiate the two conditions is unclear [99]. TRALI instead is a generally demonstrable immune-mediated syndrome which can occur following transfusion of blood or components thereof including platelets, i.v. immunoglobulins (IVIG) or fresh frozen plasma (FFP) [100]. The clinical presentation is in the form of pulmonary infiltrates and hypoxemia meeting the gas exchange definition for ARDS that develops within 8 h of transfusion [101]. Heart failure or fluid overload (TACO) must be carefully excluded [102]. In most cases, mechanical ventilation is required for a period of 12–96 h. Patient-related risk factors for TRALI include an older age, smoking, chronic alcohol abuse, an underlying inflammatory condition, sepsis, being on mechanical ventilation with elevated, potentially barotraumatic insufflation pressures, a context of recent surgery or trauma and a positive fluid balance. Blood- and transfusion-related factors include the presence in the donor pool of at least one female, generally multiparous, bearing the pathogenic antibody [101]. There is an average five-fold increased risk of TRALI if one in the donor pool has detectable anti-HLA I or II or anti HNA3 antibodies at a high titer and with a high affinity for cognate antigen in the recipient. Other factors for TRALI include 'shelf age' of the transfused blood, and maternal-to-child transfusion. Although TRALI occurs in 1/5,000–7,000 transfusions, in ICU, trauma or surgical care settings the incidence is up to 1–5 % of those transfused. 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 against a two-hit process. Factors such as sepsis, inflammation, mechanical ventilation or surgery are predisposing factors *via* pretransfusional pulmonary leukocyte sequestration. Then, transfusion of blood components containing an anti-HLA or HNA antibody triggers the full-blown TRALI reaction. This hypothesis may explain why 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 injure the pulmonary venules, causing endothelial fenestration fluid leakage and ultimately the clinical picture of pulmonary edema and ARDS [103]. An antibody directed against a cognate antigen of the recipient is identified in the donor in about 75 % (50–85 %) of TRALI cases, then denoted immune TRALI. The remainder of cases are labeled nonimmune TRALI, and 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 MODS occurs in 10–18 %. Recognition of TRALI has an immediate impact on donor selection. However prevention is 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 detection of an antibody, followed by deferral of the implicated donor from the donor pool. In a look-back study [104], out of 5 patients who received multiple transfusions from the same donor, 4 suffered relapse and only 2 of 8 severe reactions were reported to the blood safety authority suggesting that measures to defer donors may not be implemented properly. Risk reduction strategies include avoidance of unnecessary transfusions, transfusion of washed components, screening potential donors for antibodies, chosing 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 to dilute any possible antibody. Other possible complications of blood transfusions include an increased incidence of postoperative pulmonary edema and ARDS, and enhanced bleomycin pulmonary toxicity.

Acute Infiltrative Lung Disease

Several drugs and chemicals can occasion acute cellular interstitial lung disease with the gas exchange characteristics of ARDS (Table 34.6).

Acute Nonspecific-Like Interstitial Pneumonitis (Fig. 34.3)

Although nearly 70 drugs can cause acute dense cellular ILD, the most noticeable drugs include amiodarone, BCG therapy, the m-TOR inhibitors sirolimus, everolimus and temsirolimus, fludarabine, gold salts, imatinib, interferons, leflunomide, methotrexate and nitrofurantoin. Clinical presentation is with cough, fever, rapidly-progressive diffuse pulmonary infiltrates over a few days or weeks with, usually, a predilection for the dependent regions of the lung. Patients who develop this complication may show a prodromal phase of mild ILD where HRCT discloses a discreet diffuse haze, ground glass, or mosaic attenuation which can resemble hypersensitivity pneumonitis. Then the disease can accelerate without much notice if the drug is continued and sometimes despite drug withdrawal, causing acute respiratory failure that requires ventilatory support. In more advanced cases, consolidation, air bronchograms and volume loss are present with sometimes inter- and/or intra-lobular septal thickening, crazy-paving or pleural effusion. The BAL typically shows an increase in lymphocytes, with a CD8+ or, less often, CD4+-dominant pattern. But a neutrophil- or eosinophil-dominant BAL has also been reported. The BAL profile is likely to be influenced by timing of this test into the course of the disease and whether the patient has received corticosteroid therapy [105]. The BAL has an exclusionary role and it is used to discard a coincidental or drug-induced bacterial, viral, fungal, or parasitic infection. It may be difficult to separate acute drug-induced ILD from *Pneumocystis jiroveci* pneumonia. It may also be difficult to separate true pneumocystis pneumonia from acute drug-induced ILD with pneu-

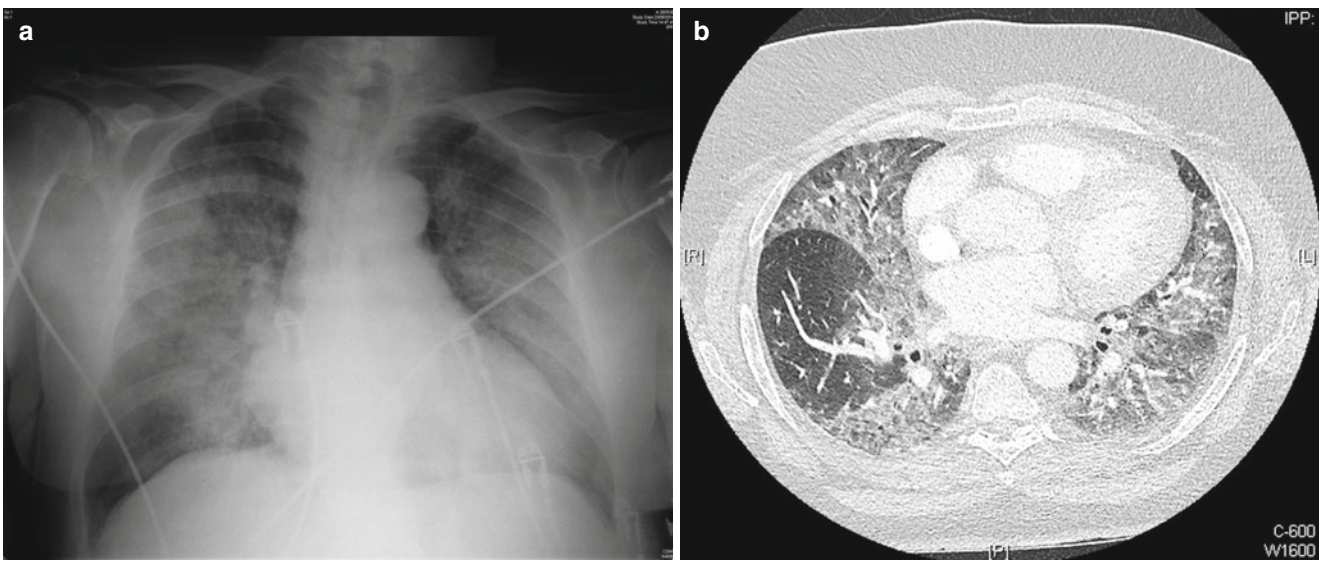

Fig. 34.3 (**a**) Amiodarone pulmonary toxicity (amiodarone lung). Corresponding CT on (**b**)

mocystis colonization when the rt-PCR pneumocystis signal is detected but no microorganisms are evidenced. Pathology discloses an interstitial inflammation with dense interstitial mononuclear infiltrate and interstitial edema. Although the lung biopsy may provide information, a risk/benefit analysis is not available and most physicians will use the BAL data and proceed with empiric corticosteroids and anti-pneumocystis therapy for those patients who have risk factors (underlying malignancy, connective tissue disease, corticosteroid therapy, recent irradiation, low circulating CD4+ lymhocytes) or an rt-PCR signal. Outcome of this form of drug-induced condition is good, with dissipation of all signs and symptoms following drug discontinuance and corticosteroid therapy. Stopping the medication alone may not result in an objective response. Corticosteroid dosage is adjusted to response with tapering over a few weeks or months. High-dose methylprednisolone boluses have become popular in the literature from Asia to treat this condition, but the efficacy of this form of therapy versus more conventional dosages is no established. Rechallenge with the drug will often lead to relapse but this is not seen in every patient without any known predisposing factor [106]. Death can follow drug rechallenge [107]. Pulmonary fibrosis following resolution of an acute ILD episode is rare, except in those patients with underlying or preexisting rheumatoid lung or idiopathic pulmonary fibrosis, which may progress after an episode of drug-induced pneumonitis [2].

Acute Granulomatous Interstitial Lung Disease

Among the 24 drugs or families capable of causing ILD with a pathology pattern of granuloma, methotrexate, intravesical BCG, anti-TNF agents and drugs of abuse can occasion a diffuse severe enough granulomatous lung disease as to cause respiratory failure with ARDS [2]. On imaging, granulomatous ILD has an established reputation for causing a miliary pattern [108] or haze [109], but in severe cases nodules tend to coalesce and can produce a rapidly-progressive white-out [110]. Other identifiable causes for granulomas should be excluded, in particular lung tissue and/or BAL fluid should be examined for bacterial, mycobacterial (*M tuberculosis*), fungal (eg *Histoplasma*) and parasitic infection. The quest for diagnosis is both patient- and country-dependent as certain microorganisms have a predilection for a specific geographical distribution (e.g.: *Histoplasma, Cryptococcus, Blastomyces, Coccidioidomyces*), or are more common in patients with a given underlying condition (e.g. *Pneumocystis* and CTD, immunosuppressive drugs, radiation therapy or corticosteroid therapy). Other causes for pulmonary granulomas include environmental agent (bird droppings, beryllium, hot-tub), aspiration of food particulates, sarcoidosis, ANCA-related granulomatosis and vasculitis (formerly known as Wegener's) and rheumatoid lung nodules [111–113]. Central necrosis of the granulomas makes infection a more likely diagnostic consideration, as this seldom is seen in methotrexate lung [114]. Issues raised by the four aforementioned drugs differ substantially.

A fraction of patients on longterm methotrexate (incidence estimates have dropped from 3 to 0.5 % nowadays) [115] develop an acute granulomatous pulmonary reaction without any convincing feature for an infection [116]. Lymphocytes are increased in the BAL in some but not all patients [117]. A confirmatory lung biopsy is rarely performed nowadays. However, ruling out pneumocystis pneumonia by immunofluorescence and molecular techniques is vital as pneumocystis pneumonia may assume a granulomatous pattern of reaction [118] and has a less favorable an outcome, as compared to when it occurs in HIV-positive individuals. A review of the pathologic features of methotrexate pneumonits indicated granuloma formation in 35 %, giant cells in 26.5 %, and tissue eosinophils in 18 % [114]. In 8 % of the biopsies, diffuse alveolar damage was present [114]. ARDS in methotrexate lung may be caused by extensive interstitial lung disease with or without granulomas and superimposed DAD, pulmonary edema or DAH. Management of all these forms is similar and consists in corticosteroid therapy and supportive care including mechanical ventilation where needed. Mortality is 16 % overall. Relapse rate is 25–50 %, and death may occur in as much as half those who relapse [107].

Treatments of bladder carcinoma with topical intravesical BCG lead to an acute pulmonary granulomatous reaction in about 3 % of those so treated. In most patients, the disease is self-limiting but in some, fever and acute respiratory failure develop. Some cases correspond to hypersensitivity and in those, corticosteroid therapy is indicated and efficacious. In a few patients pulmonary granulomas correspond to true BCG infection as *M bovis* molecular imprints are present in the tissue. In those patients, antituberculous chemotherapy is indicated in addition to corticosteroid therapy.

Anti-TNF can occasion systemic granulomatous disease resembling sarcoidosis, the disease has an indolent course in nearly all patents [119, 120]. An acute granulomatous pulmonary reaction should prompt the diagnostic consideration of miliary tuberculosis or granulomatous pulmonary infection (depending on country), conditions to which anti-TNF, particularly infliximab, predispose [121, 122]. This may occur even though patients tested negative for LTBI prior to commencing treatment with these agents as new infection can be acquired at any time [123].

Intravenous abuse of crushed tablets of drugs intended for oral use including methadone pills may elicit a granulomatous response in the form of talc, crospovidone, starch or cellulose foreign body granulomas, a peculiar and aggressive form of foreign body reaction in the lung [124, 125]. Pathologic examination with special stains and X-ray

analysis of lung tissue help identify the foreign material [126]. Depending on route of administration, tissue response can center on airways or vasculature, causing obliterative bronchiolitis or -vasculitis with obstruction to airflow, pulmonary emphysema, lung bullae pulmonary hypertension or venoocclusive disease, respectively. Patients may present acutely as the disease can accelerate without any apparent reason or under the influence of concomitant HIV-related pulmonary infection. Funduscopic examination in longterm addicts may disclose small sized foreign bodies that bypassed the pulmonary circulation [126].

Acute eosinophilic pneumonia (AEP) (Fig. 34.4)

AEP has been reported with 28 separate drugs, mainly the antibiotics minocycline and daptomycine, the antimalarial chloroquine, antidepressants and inhaled drugs and substances (cannabis, heroin, incense, or recent onset of exposure to tobacco smoke) [2]. Drugs that cause AEP overlap with the 148 which cause eosinophilic pneumonia [2], suggesting that AEP and eosinophilic pneumonia are closely related diseases running a different course, AEP representing the upper end of the severity spectrum of eosinophilic lung disease. Acute eosinophilic pneumonia is a febrile illness that develops acutely and culminates with hypoxemic respiratory failure, diffuse white-out, ARDS and pleural effusion. Mechanical ventilation is required for some days in the majority of affected patients. A few patients have necessitated ECMO [127]. BAL eosinophils above 25 % is the rule and figures above 50 % are common. Blood eosinophilia can be in the normal range, particularly in patients who have progressed rapidly or who have received a recent course of corticosteroids. For the diagnosis to be considered, parasitic or other infection, notably with *Strongyloides stercoralis* should be ruled out. Massive BAL eosinophilia obviates the need for a confirmatory lung biopsy. Eosinophils in the absence of an infection portend potentially reversible disease. The pattern of involvement on pathology is in the form of tissue eosinophils on a background of mononuclear cell infiltrate and acute and/or organizing diffuse alveolar damage [128]. Hyaline membranes are an unusual finding in this condition. Discontinuation of the drug or stopping exposure to cigarette or marijuana smoke is the mainstay of management. Corticosteroid therapy is indicated in the majority or patients. Outcome is good.

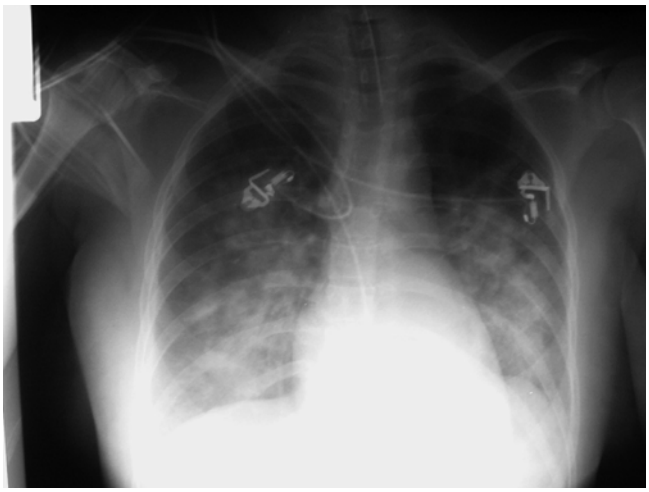

Fig. 34.4 Pulmonary edema

Recent evidence suggests that in addition to drugs with a limited base of evidence, cases of eosinophilic granulomatous with polyangiitis (GPA; Churg-Strauss) may develop with therapy with leukotriene receptor antagonists (LTRA) or omalizumab. To get a full understanding of the causation in each patient, one has to take into account the increased background rate of GPA in asthma, the fact that corticosteroid therapy may have been tapered or withheld recently in patients who are started on LTRA and/or that introduction of LTRA may herald more severe asthma. Notwithstanding these lines, there seems to be undisputable cases of LTRA-associated eosinophilic angiitis, and this is also supported by some [129] but not all epidemiologic studies [130]. At any rate, withdrawal of LTRA or omalizumab should be considered in the patient on LTRA who presents with new onset GPA.

Acute organizing pneumonia (OP)

Most OP cases are idiopathic and named cryptogenic or COP. Ninety therapy drugs, radiation, excipients and abused drugs have been cited as causes for organizing pneumonia [2]. Drugs and substances of abuse account for up to a third of biopsy-proven OP cases [131]. Nine percent of iatrogenic OP cases are fatal from uncontrollable respiratory failure, a figure similar to idiopathic OP. Practically, evidence for causality is heterogenous and often limited, as authors sometimes use solely imaging (OP *sine* pathology) or rely on a transbronchial lung biopsy specimen showing a few alveolar buds of connective tissue. Assessment of drug causality is also problematic as OP can occur as a spontaneous manifestation of hematologic malignancies, stem-cell transplantation, connective tissue disease, inflammatory bowel disease, pneumonia or idiopathically. The diagnosis of therapy-related OP is entertained in the patient with migratory pulmonary opacities or diffuse white-out on sequential imaging or a confirmatory histopathologic diagnosis of OP, in the absence of significant BAL eosinophilia, with exposure to a compatible drug, abatement of all signs and symptoms following drug discontinuance with or without corticosteroid therapy and lack of relapse over a follow-up period. Recently, the acute fibrinous

organizing pneumonia or AFOP pathologic pattern has been described, and has now been reported in association with 9 distinct drugs [2]. This OP variant is characterized by a dominant pattern of intraalveolar fibrin, fibrin balls and organizing pneumonia [132]. Organizing pneumonia or AFOP cases diagnosed on pathology may represent the resolving phase of acute lung injury/diffuse alveolar damage. AFOP carries a worse outcome as compared to OP, as 9 of the 17 patients by Beasley *et al*. died from the condition [132], a rate similar to outcomes in DAD. Evidence that drugs actually cause AFOP is limited. One of the 17 patients described by Beasley was being treated with amiodarone DAD, and two recent AFOP cases occurred in patients who were being treated with a statin drug [2]. The practical implication is that readministration of any suspect medication after recovery from an AFOP episode should be discussed very carefully, lest fatal relapse may supervene.

Accelerated Pulmonary Fibrosis

Chemotherapy agents including bleomycin and rarely methotrexate may cause acute progressive pulmonary fibrosis [2]. This condition may occur following an acute episode of chemotherapy lung or acute NSIP-like ILD, or it occurs months after completion of therapy. In a few cases, oxygen or radiation therapy seemed to synergize chemotherapy or amiodarone and triggered the onset of pulmonary fibrosis running an accelerated course. Amiodarone pulmonary toxicity can manifest as acute lung fibrosis progressing rapidly to respiratory failure and death despite drug withdrawal and corticosteroid therapy. Anti-TNF agents may also cause rapidly-progressive acute lung fibrosis [2, 133, 134]. Schuller et al. [135] reviewed 42 rheumatoid arthritis patients including 2 on their own, who developed acute ILD while being treated with anti-TNF agents (infliximab, 24, Etanercept 15, adalimumab 3). Etanercept cases tended to present with a granulomatous reaction and to have better outcomes, while infliximab cases demonstrated a 'UIP' pattern and had a worse prognosis.

Acute Amiodarone Pulmonary Toxicity (Fig. 34.5)

A fraction of patients with amiodarone pulmonary toxicity (APT) may present acutely, in the form of diffuse white-out and acute respiratory failure [136]. The drug is now considered a strong risk factor for ARDS [18, 137]. In very few patients, acute APT is in the form of dense NSIP-like ILD after a few weeks on the medication, as opposed to the slowly-progressive indolent course of classic APT [138]. Such acute NSIP-like APT cases in ambulatory patients present with diffuse haze or ground-glass, elevated lymphocytes

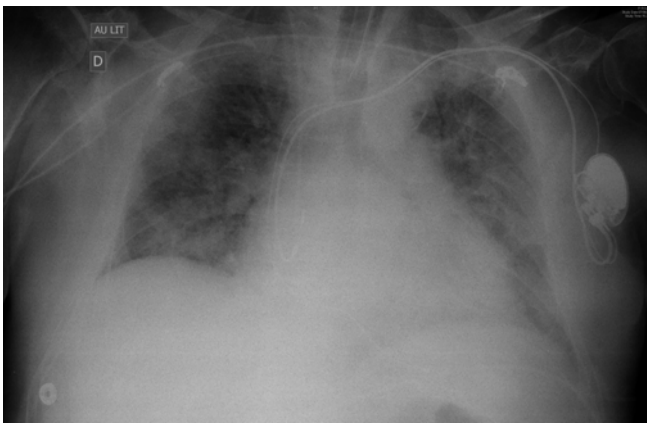

Fig. 34.5 Alveolar hemorrhage

in the BAL and a demonstrable response to corticosteroid therapy. Most acute APT cases occur however postoperatively after cardiac, coronary bypass graft or thoracic surgery in the form of ARDS [139]. Notable features include onset within a few hours or days of cardiovascular or thoracic surgery in a patient who was chronically treated with amiodarone, or who received as little as 1,100 mg of the drug postoperatively [140]. In one study, prophylactic amiodarone was given to combat supraventricular fibrillation that commonly occurs after resectional thoracic surgery [141]. This led to a six-fold increased incidence of ARDS with an 66 % attendant mortality, but not all studies confirmed that point [142]. A *postmortem* study in amiodarone-associated ARDS cases showed that it may take as little as two days on the drug to develop endogenous lipoid pneumonia and foam cells that characterize APT on a background of DAD [140, 143]. Foam cells can also be retrieved in the BAL fluid of such patients. The response of amiodarone-associated ARDS to corticosteroid therapy is uncertain, but corticosteroids are considered good practice if other causes for postoperative ARDS have been excluded (Fig. 34.4). The role of intraoperative factors has been advocated. Single lung ventilation with oxygen during a surgical procedure has led to selective damage of the ventilated lung while the 'resting' lung was spared [144]. An intriguing feature of those who survive an episode of amiodarone-associated ARDS is that they were restarted on amiodarone after surgery without recurrence. This finding emphasizes that amiodarone-associated ARDS may involve an interaction between amiodarone and peri- or intraoperative factors such as elevated dioxygen tension, barotrauma, cytokine release, or surgical lymphatic damage. The practical conclusion from these studies is that liberal or prophylactic use of amiodarone and above-needed inspired oxygen tension during the intra- and post-operative period should be avoided, amiodarone after thoracic surgery being reserved for symptomatic arrhythmia cases. Two previously unreported patterns of APT were described recently in 12

patients (among 75 APT cases, overall) exposed to amiodarone longterm (range 1–12 years): lymphoid hyperplasia was diagnosed in eight cases, including diffuse lymphoid hyperplasia, follicular bronchiolitis, lymphoid interstitial pneumonia, and lymphocytic perivascular cuffing [145]. Features of AEP including diffuse alveolar damage with eosinophils were present in two cases [145]. Two showed features of chronic eosinophilic pneumonia [145].

Diffuse Alveolar Hemorrhage (Fig. 34.6)

Diffuse alveolar hemorrhage (DAH) corresponds to the egress of fresh blood from the normally leaktight pulmonary circulation [146]. Bleeding in the deep lung causes alveolar filling, shortness of breath, diffuse haze or ground-glass, pulmonary infiltrates, hypoxemia and anemia. Even though DAH may be suspected on the basis of batwing or diffuse fluffy opacities on imaging and CT, the condition may stay undiagnosed unless BAL is performed. The BAL is the key diagnostic tool for this condition when it shows a progressively bloodier return on sequential aliquots [147]. Hemoptysis and an increase in the diffusing capacity for carbon monoxide are not constant features of this condition [146]. A significant abrupt drop in hemoglobin characterizes those cases with severe bleeding. Additional severity may stem from extent of bleeding or clotting in the distal lung and/or airways which may lead to the stone or locked lung respectively, retention of the compound (e.g. brodifacoum) in the body causing further or persistent DAH, underlying condition (e.g. solid or hematologic malignancy) and response of DAH to management. Alveolar hemorrhage can be isolated and is then called bland DAH, or it occurs in conjunction with extrapulmonary features such as skin involvement, microscopic hematuria, renal failure, heart and/or other organ involvement and/or circulating ANCA of various specificity or ANA of mechanistic relevance. Drug-induced DAH can mimic both the clinical manifestations and the laboratory features of systemic ANCA-related vasculitis, *lupus*, or Goodpasture pneumorenal syndrome. The merit of the lung biopsy compared to BAL is unclear. Even though the biopsy may evidence pulmonary capillaritis in addition to DAH, whether this finding does refine management of this condition as compared to a more conservative approach is unclear. History taking in patients with DAH includes exposure to hydrocarbons, crack cocaine, marijuana or tobacco smoke or fumes of snorted crack cocaine or heroin, pesticides, such chemicals as brodifacoum or paraquat, hyaluronate and silicone [2]. Early urine screen for abused drugs (to be interpreted according to whether the patient has taken or been given fluids) and the presence of brodifacoum [148] or paraquat [149] in blood is indicated. Therapy with 103 specific drugs has been associated with bland DAH [2]. Drugs that induce bland DAH include compounds which interfere with the coagulation cascade or platelets, namely glycoprotein IIB/IIIA inhibitors of the chemical (abciximab, clopidogrel, eptifibatide, ticlopidine, tirofiban) or biologic type (abciximab), vitamin-K antagonists, heparin, thrombolytic agents

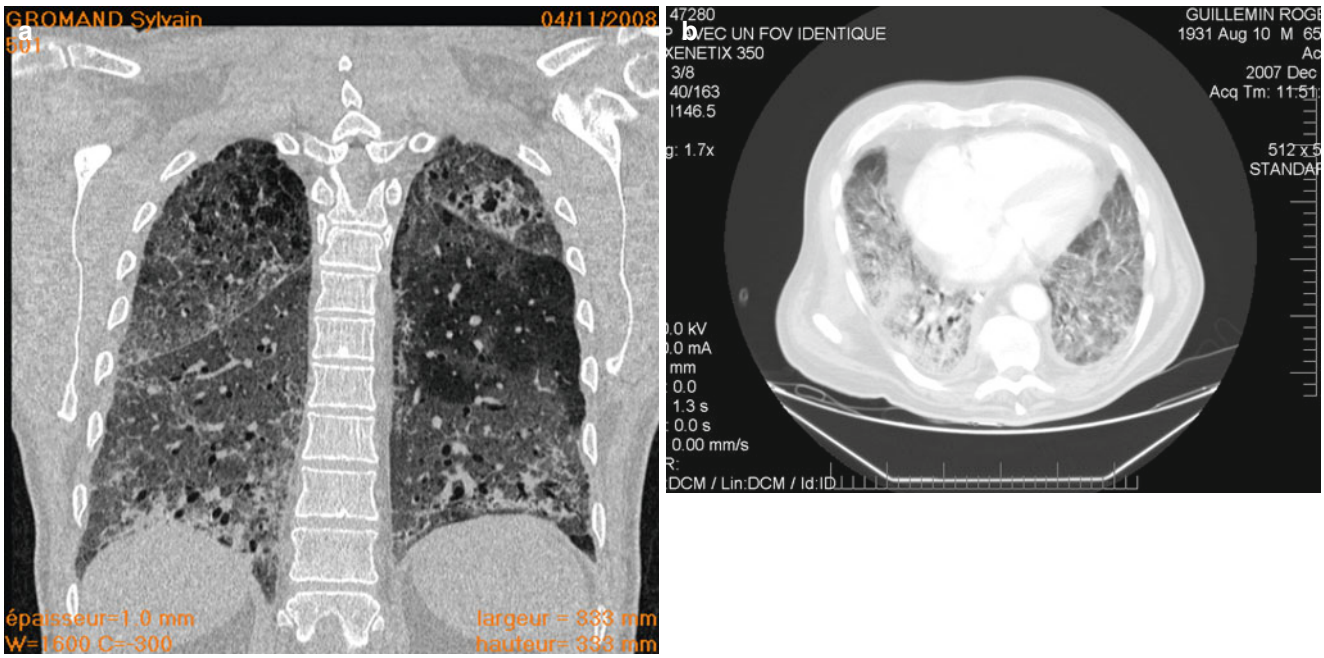

Fig. 34.6 (**a**) ARDS with probable diffuse alveolar damage, some pulmonary edema and inflammation (Bleomycin lung). Corresponding CT on (**b**)

and direct (new) oral anticoagulants. Other drugs include antithyroid drugs (carbimazole, methimazole, propylthiouracil), m-TOR inhibitors (everolimus, sirolimus), cocaine and the adulterant levamisole, acute promyeolocytic leukemia therapy with all-transretinoic acid (ATRA) or arsenic trioxide (As2O3), dextran-70 and penicillamine. Seven drugs have been associated with ANCA-related DAH and 10 with Goodpasture-like syndrome [2]. Agranulocytosis and infection characterize those cases with exposure to propylthiouracil or cocaine-levamisole [2]. DAH can occur without notice or following percutaneous coronary intervention and is easily mistaken for pulmonary edema unless the BAL is performed. Incidence is 0.2–0.9 % of those exposed to the drug depending on the compound. Risk factors include a history of smoking, myocardial infarction, an older age, concomitant therapy with heparin, and the presence of underlying COPD or left ventricular dysfunction. Thrombocytopenia, a known complication of this class of medications, is generally absent in DAH cases. The role of other medications which can also produce DAH (amiodarone, anticoagulants, aspirin, heparin, hydralazine, thrombolytic agents, sildenafil) needs be carefully evaluated and more than one drug may need to be withdrawn. Reported mortality in this particular form of DAH is 30–50 %.

Although brodifacoum (4-hydroxycoumarin) is not a drug, it is covered here as a dreadful chemical capable of causing devastating disease in children and adults. Brodifacoum is a superwarfarin that blocks the vitamin K1 cycle. Superwarfarins are also vascular-damaging agents. Rodents fed pellets containing the compound die from uncontrollable internal bleeding. Cases of accidental brodifacoum poisoning have been described in nontarget populations (companion animals, humans, birds) and the clinical characteristics are similar across all species. Cases of brodifacoum poisoning in humans have included accidental (factory workers, children), deliberate (suicidal, Munchausen syndrome), criminal, 'without-knowing' smoking of crack cocaine or marijuana adulterated with brodifacoum, and 'impossible-to-track' exposures. The diagnosis of brodifacoum poisoning should be raised in any unexplained severe bleeding or DAH case with profoundly altered coagulation studies. Brodifacoum can be measured and followed serially in blood and its extended biological half-life of 1–2 months (depending on metabolic trait) accounts for the persistent coagulopathy that may require vitamin-K replacement therapy for up to 1 year. Clinical presentation of brodifacoum poisoning is with epistaxis, hematemesis, DAH or neurologic symptoms depending on the preferred site of bleeding. Laboratory features include prolonged prothrombin and activated thromboplastin time 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 (which may produce TRALI as a second-hand complication) and vitamin-K. However, relapse of bleeding and DAH can occur due to the slow elimination kinetics of the compound requiring prolongation of vitamin K replacement therapy until coagulation returns to the normal range. Though the majority of brodifacoum poisoning in humans are non-fatal, forensic pathologists and veterinarians can be confronted with brodifacoum-related deaths from massive DAH and internal hemorrhage.

Fluid silicone or hyaluronate are injected by cosmetic surgeons or 'lay' operators during illicit clandestine surgery sessions by for the purpose of cosmetic skin, mammaplasty or body augmentation through injections in the gluteal region or the buttocks, sometimes in the context of transsexualism [150, 151]. Part of injected silicone may access and embolize to the pulmonary circulation, causing the silicone embolism syndrome (SES), acute lung injury, ARDS and DAH. The SES shares several clinical and imaging features with fat embolism, including the possibility of migration to the central nervous system through unidentified shunts, where silicone can cause life-threatening neurological impairment [150]. The silicone syndrome develops within minutes-to-a few hours of the procedure. Shorter delay times portend greater severity. Clinical presentation is with any combination of fever, dyspnea, nonproductive cough, chest pain, hypoxemia, hemoptysis, petechiae and obtundation [150]. Imaging studies include bibasilar or diffuse infiltrates and CT studies demonstrate subpleural basilar or diffuse areas of alveolar shadowing or consolidation [150]. Suggestive changes on CT may indicate of silicone injection in the breasts. BAL examination can reveal silicone vacuoles in macrophages or in multinucleated giant cells in the form of large, pleomorphic, cytoplasmic inclusions on a background of neutrophils and hemorrhage [152]. Pathology of the lung shows nonstainable (except if oil-red-0 staining is prolonged for 72 h) interstitial vacuoles with a peripheral refractile meniscus of silicone on dark field microscopy [152]. The silicone droplets conform to the shape of pulmonary capillaries. Energy dispersive X-ray analysis can confirm the chemical composition of silicone. Outcome of SES is good except in patients with injection of large amounts of silicone, an early onset of symptoms or a neurologic presentation, who sustain very high mortality [150].

Inhalation or, rarely, injection of straight cocaine may be followed in a few hours by an acute episode of DAH. In one study, cocaine accounted for 12 % of DAH cases admitted to the hospital. Figures may be higher as history taking in intoxicated patients can be suboptimal and patients often are reluctant to give a real abused drug history [153]. DAH is a common finding in autopsy lungs of fatal drug addict cases, being present in 58 % in one study [154]. DAH caused by cocaine has a wide spectrum of severity. On the low end, most crack cocaine users exhibit subclinical DAH in the form of hemosiderin-laden macrophages in the BAL. On the

high end, both cocaine and crack cocaine smoking can cause clinically-manifest sometimes massive DAH that appears to be limited to the lung. In addition, the etiology and clinical presentation of cocaine-associated DAH has changed in the recent past, as most cocaine samples in the US 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 antihelminthic or deworming agent. Pharmaceutical grade levamisole purportedly enhances the euphoric effects of cocaine [155], but mainly poses a risk of neutropenia, agranulocytosis, skin necrosis and deep-seated organ involvement [49]. These changes have been described in the 1970s, and there has been a resurgence of similar such cases recently in levamisole-laced cocaine users. Cocaine-levamisole toxicity manifests more often with crack cocaine inhalation than with cocaine snorting. It is 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 skin of the limbs [156]. These manifestations may correspond to true vasculitis with IgM, IgA, IgG, and C3 deposits or more often to focal thrombotic vasculopathy with intravascular fibrin formation leading to occlusion and ischemic skin necrosis. The skin involvement may be extensive requiring reconstructive surgery [157]. Notable laboratory features include neutropenia (<3,000) or agranulocytosis which constitutes a relevant risk factor for superimposed infections [158], and auto-antibodies (speckled antinuclear antibodies, anticardiolipid antibodies, ANCA often 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) [12]. Concomitant positivity to both MPO and PR3 (100 and 50 % in one series, respectively) is suggestive [12]. Rare reports mentioned anti-double-stranded DNA. The panoply of pleiomorphic antibody positivities at high titers should draw attention to the drug etiology. DAH develop in a fraction of poisoned patients and was recently noted in 3 of 30 cocaine-levamisole toxicity cases. Other organ damage was present in the form of ENT involvement or sinusitis (possibly due also to cocaine snorting) in 44 %, kidney injury in 8 (severe in two, with evidence of pauci-immune glomerulonephritis in one), and vasculitis in 3. Clinicians may be able to clue in on the correct diagnosis of cocaine-levamisole toxicity in view of the characteristic skin changes, neutropenia and ANCA antibodies that are now part of the evaluation in the patient with exposure and the appropriate skin changes. In view of these manifestations, an algorithm has recently been proposed in patients with cutaneous involvement that would also apply to any DAH case in a patient suspect of being a cocaine-user, starting with cocaine urine screen which, if negative, is followed by GC/MS measurement for levamisole in urine only if the clinical suspicion of levamisole toxicity is strong [159]. The next step is ANCA measurement 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 may also suggest the presence of cocaine and levamisole [159].

The antithyroid drugs propythiouracil (PTU), benzythiouracil and methimazole can also produce a form of vasculopathy that is not dissimilar to that induced by levamisole [2]. Patients who are on PTU for at least a few weeks present with any combination of neutropenia or agranulocytosis, necrotic skin changes or gangrene, and pathologically-demonstrable eosinophilic or neutrophilic vasculitis. As with levamisole, patients present with violaceous skin changes, vasculitis in the skin, pinna or limbs, and in a subset DAH develops [160]. Patients typically have elevated ANCA titers. Importantly, ANCA are rarely elevated in untreated Grave's disease and are strongly associated with therapy with antithyroid drugs of any significant duration (this finding that cannot be assessed in cocaine-levamisole-exposed abusers as data on drug exposure is unreliable). Both perinuclear or, less often, cytoplasmic moderately elevated ANCA titers develop in 33–50 % of patients chronically treated with propythiouracil or benzylthiouracil [161]. The majority of such patients have no symptoms nor do they develop clinically demonstrable disease. Consequently, propythiouracil needs not be discontinued in such patients who, however, need be monitored as regards ANCA titres and educated as regards the possible development of symptoms suggestive of vasculitis in the future. Acute DAH or other forms of pulmonary, pleural, pericardial or extrathoracic manifestations of systemic vasculitis may develop after several more months into treatment in about 2.5 % of them. ANCA with specificity to more than one lysosomal antigen constitute a distinctive serological profile antithyroid drug-related ANCA. The p-ANCA exhibit MPO or dual MPO- and PR3 staining and anti-lactoferrin, -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 [162]. One study addressed the issue of ANCA specificity and titers among 250 ANCA-positive cases [162]. Thirty of these 250 (12 %) had very high (>12-fold above the median of the 250 patients) anti-MPO titers and all of these 30 had clinical features of vasculitis. Ten of these 30 had been exposed to hydralazine, 3 to propylthiouracil and 5 to penicillamine, allopurinol, or sulfasalazine. There was a strong association between the presence of anti-neutrophil elastase and/or anti-lactoferrin antibodies and exposure to one candidate drug [162]. Thus, therapy with antithyroid drugs, or hydralazine

should be sought in cases of vasculitis coexisting with high ANCA titers. From 25 to 60 % of patients on propythiouracil who happen to develop overt ANCA-related disease or vasculitis have pulmonary involvement, typically in the form of DAH with or without histologically demonstrable capillaritis. Tissue granulomatous inflammation and necrotizing inflammation have also 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 propythiouracil-related as opposed to idiopathic ANCA-related renal disease [163]. Terminal renal failure is noted in about 5 % [164]. Overall, mortality is approximately 15 %, with a few patients dying from uncontrollable DAH [164]. Patients with the most severe involvement will necessitate induction therapy with corticosteroids, cyclophosphamide and plasma exchange in a manner similar to idiopathic vasculitis and DAH. 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 evidence for disease.

Contrasting with idiopathic *lupus*, DAH is very unusual in the drug *lupus*.

Anti-basement membrane-related DAH (Goodpasture's) once was considered an idiopathic condition. However, a study of 28 carefully-documented Goodpasture cases showed that 89 % of the patients were smokers, and 36 % gave a history of exposure to inhaled cocaine, cannabis or heroin [165], raising the possibility that Goodpasture may be triggered by drugs and chemicals.

Such drugs as TNF antagonists, procainamide, levamisole and interferon have been associated with circulating antiphospholipid/antisynthetase- antibodies or syndrome [2].

Exacerbated Pulmonary Fibrosis

Some patients with idiopathic (IPF) or connective tissue disease-related ILD develop unexpected rapid or precipitous decline in pulmonary function, in the context of diffuse pulmonary infiltrates, progressive respiratory failure and ARDS. This condition is usually named 'acute exacerbation' of pulmonary fibrosis which, by definition, is not due to any recognizable factor. Yet, drugs and vaccinations have been cited at the origin of such 'acute exacerbations'. Three of the nine patients described by Parambil et al. as having an acute exacerbation were being exposed to drugs capable of causing acute ILD, namely azathioprine in two and leflunomide in one [93]. The same group reported on 58 pathologically-confirmed DAD cases, of which 15 had pulmonary fibrosis. Drugs (blemycin, aracytine, gemcitabine, cocaine, amiodarone) had caused the acute deterioration in 6 cases, and radiation therapy in one [94]. Likewise, 42 rheumatoid arthritis patients were recently reviewed, who developed acute pulmonary deterioration while receiving TNF-alpha inhibitors, and these drugs were thought to have caused the deterioration [135]. On the other hand, rheumatoid arthritis-associated ILD (the rheumatoid lung) is classically considered a relevant risk factor for severe episodes of acute methotrexate pneumonitis [166]. Instances of fatal deterioration of previously-diagnosed indolent pulmonary fibrosis have also been reported in lung cancer patients exposed to chemotherapy drugs or different TKI [167–169]. In addition, drugs with significant potential for causing pulmonary toxicity (e.g. amiodarone, statins [2]) are likely to be given to the population with smoking-related or idiopathic pulmonary fibrosis, owing to age-related heart and coronary artery disease. When in doubt, withdrawal of any potentially toxic drug is indicated in the pulmonary fibrosis patient whose disease exacerbates. Influenza vaccination is also suspected to cause acute deterioration of IPF [2].

Acute Vasculopathy Causing ARDS

Diffuse withe-out and the clinical syndrome of ARDS may result from iatrogenic or self-induced intravenous injection and embolization of foreign material into the pulmonary circulation. Examples include, the excipient DMSO, fluid silicone, bone marrow, blood and components, calcium replacement therapy, liquid or elemental mercury, 'inert' drug excipients or solvents, colony stimulating factors, aprotinin, protamine, gas from hemodialysis or the ECMO machine setup, fat or lipids (propofol, parenteral nutrition, mineral lipids) [2]. Consequences include vascular obstruction, injury from sharp-edged embolized material, activation of the coagulation cascade, pulmonary intravascular coagulation followed by fluid leakage. A history of recent injection or infusion of drugs including drugs of abuse, surgical procedure, liposuction and the patient should be examined as regards telltale venous access sites or paraphernalia.

Methylmethacrylate cement embolism is a distinctive complication of vertebroplasty sessions [2]. During kyphoplasty, acrylate cement is injected into the vertebral body. Leakage of cement and bone marrow occurs in up to a quarter of the patients and this is symptomatic in about 5 %. The condition is of interest to the radiologist and interventional radiologist. Embolized cement is in the form of tubular, branching, punctuate or wormlike dense pulmonary opacities corresponding to cast cement within pulmonary arteries [170, 171]. This is best viewed on plain chest radiograph and unenhanced CT. Fatal embolism can follow high volume acrylate polymerizing during transit through the heart or main pulmonary arteries [172].

Transhepatic chemoembolization sessions may be complicated by spillage of doxorubicin, cyanoacrylate with or without iodized oil (Lipiodol), causing pulmonary embolism, pleural effusion, acute pulmonary edema and ARDS within hours of the procedure [173].

Although ARDS cases have become rare following radiation therapy to the chest particularly since the advent of novel stereotactic techniques and establishment of relatively safe radiation thresholds, the complication is now almost exclusively reported in patients who receive concomitant irradiation and chemotherapy. A series of 15 patients with ARDS developing after systemic administration of the radiochemical 131I for the treatment of hepatocellular carcinoma has been reported and was fatal in 12 [174].

Drug-Induced Airway Emergencies

Angioedema episodes, of which about 70 % occur in patients exposed to a drugs is the most common and worrisome complication of drugs [2]. Angioedema may develop concomitant with generalized anaphylaxis, or it occurs in isolation, sometimes after months or years on the medication without any adverse effect. The condition causes rapidly progressive upper airway obstruction (UAO) and asphyxia [175]. Epidemiological studies evidence an increased incidence of this complication [176]. Drug-induced UAO 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 [177, 178]. Incidence of angioedema is less than (about 1/30th) and has no relationship with ACEI cough. As for ACEI, the incidence is greater with enalapril and lisinopril as compared to captopril, and ARB-associated UAO it is about 1/10th–to-1/20th compared to ACEI-related UAO, both greater than the background incidence in unexposed subjects. Mild grades of angioedema are notoriously underdiagnosed, and the prolonged consequential delay times patients spend on continued exposure to the drug despite repeated episodes of lip, tongue, mouth, mouth floor or throat edema puts them at risk of developing a fatal episode of major airway blockage and asphyxia. Risk factors include a disproportionate four-fold greater incidence in African-Americans or Afro-Caribbeans compared with Caucasians, which accounts for a greater incidence of this complication in the US [179]. Airway manipulation and trauma of intubation are recognized risk factors, although UAO may develop unexpectedly with no identifiable trigger. Anesthetists and emergency physicians are on the frontline, as they may be confronted with this dreadful complication at any time. Angioedema is more likely to occur in the first few weeks of treatment in dark-skinned people while in whites, it may occur up to a few years into treatment. About 25 % of patients give a history of previous spontaneously resolving episodes of oral edema which failed to be identified as drug-related. Early warning symptoms include a sore throat, drooling of saliva, dysphagia, pruritus [180] and this is followed by the rapid development of edema of the lips, floor of the mouth and/or larynx. Type 1 angioedema corresponds to edema limited to the face, type 2, to mouth floor, base of tongue and uvula, and type 3 oropharyngeal, supraglottic and glottic, rarely involving the thoracic trachea. The risk of asphyxia is greater in patients with the type 2 or 3 angioedema, and these are more liable to experience breathing difficulties and to require admission to the ICU or needing intubation. It is important to identify and secure the airway early, using the fiberoptic bronchoscope and/or tube as if the edema progresses, complete airway obliteration may occur, identification of the airway can prove impossible, and traumatic cricotomy or tracheostomy is perilous in the context of impending asphyxia and anoxia, and irreversible hypoxic brain damage may lead to the patient's demise [181]. A few angioedema cases are complicated by laryngospasm with negative pressure pulmonary edema or hemorrhage as a secondary complication (see below under NPPE). About 40 % of patients require ICU admission and mechanical ventilation is indicated in 10 % overall. Patients need be monitored for an average of 2 days, as rebound angioedema can occur despite drug discontinuation. Corticosteroids and histamine have unproved efficacy. The bradykinin B2 receptor inhibitor icatibant has met with success in reducing the time to recovery from 33 to 4.4 h [182]. Other therapy drugs of interest include ecallantide, fresh frozen plasma, C1-inhibitor and II-VII-IX-X concentrate [182, 183]. Repeated education of patients started on ACEI and ARB is crucial. Rechallenge is hazardous as severe or fatal UAO may recur after variable time on the medication [184]. There has been a few cross-reactions with UAO from both ACEI and ARB in separate occasions in the same individual.

Anaphylaxis is an explosive, generally unanticipated reaction that appears to be drug-induced in about 30 % of the cases [185]. Insect stings, food and exercise are other significant triggers. About 150 drugs can cause the syndrome including antibiotics, NSAIDs, gadolinium-based and radiocontrast media, muscle relaxants, immunotherapy, oxaliplatin and biologicals particularly most monoclonal antibodies and soluble receptors used to treat rheumatoid arthritis (infliximab, etanercept), hematologic and solid malignancies, cetuximab and omalizumab [2]. Incidence, time to onset, populations at risk and the risks of rechallenge are not equal with all monoclonal antibodies [186]. Cetuximab poses interesting though potentially severe risks in residents of the south eastern Unites States where tick bite predisposes to the risk of cetuximab hypersensitivity and anaphylaxis [187]. Parenteral administration of drugs expose to a greater risk as compared to oral administration. Atopy is a risk factor. A recent mul-

ticenter study of anaphylaxis due to drugs given during a hospital stay found 184 cases [188]. The 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. 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 and/or lower airway obliteration, cardiovascular collapse, shock, cramping, loss of consciousness, seizures and pulmonary edema. Drugs and food account for the bulk of causes of fatal anaphylaxis. Time to cardiac or respiratory arrest and death is within 5 min of drug administration and although a fraction of the patients are resuscitated, death from irreversible hypoxic brain damage can occur [189]. Epinephrine (adrenaline) is life saving and should be given intramuscularly 0.01 mg/kg to be repeated every 1–5 min to most symptomatic patients along with large amounts of fluids [190]. However, epinephrine may not be given early enough or in sufficient amounts before the arrest [189]. Adrenaline portends its own risks as patients may develop adrenaline-induced acute systemic hypertension, pulmonary edema or myocardial infarction [2]. Any physician should be prepared to diagnose and manage this potentially devastating complication of treatments with drugs. Elevation of the legs and avoidance of the sitting posture are paramount along with supportive measures and oxygen therapy or mechanical ventilation.

Life-threatening catastrophic bronchospasm may develop following exposure to many oral or parenteral drugs including adenosine, analgesics, antibiotics, beta-blockers, lidocaine, NSAIDs and salicylate, cocaine and crack cocaine, heroin and, less commonly about 30 miscellaneous other drugs including corticosteroids. Most of these drugs are contraindicated in patients with asthma, particularly if severe at baseline. Drugs cause more severe asthma attacks compared to other triggers. In the study by Picado et al. 8 % of acute asthma attacks requiring mechanical ventilation in the ICU were triggered by NSAID [191]. A history of severe, unstable difficult-to-control, corticosteroid-dependent asthma, atopy, nasal polyps, drug allergy or prior reaction with the same or similar drugs or congeners are risk factors. Though catastrophic bronchospasm may develop in a subject free from any prior asthma or bronchospasm (for instance with ß-blockers) [192], the complication generally occurs in patients with previously diagnosed asthma. Contrasting with drugs to which patients become sensitized upon repeated exposure (for instance oxaliplatin or omalizumab) [193], 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 and intermittent watery nasal discharge, difficult-to-treat asthma and intolerance to NSAID of the COX-1 inhibitor type and aspirin. Exposure to NSAIDs or aspirin is followed within minutes to a few hours by an increase in nasal symptoms over baseline and bronchospasm which can be severe [194]. Avoidance of any COX1 NSAID including aspirin is mandatory. Nevertheless, desensitization or a state of tolerance using incremental dosages of the causal drug may be achieved if patients need to be treated again with these medications [195–197]. However, continued exposure to the drugs 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 severe asthma attack. The vast majority of patients with aspirin/NSAID-exacerbated sensitivity are able to tolerate selective COX-2 inhibitors, though prudent challenge is recommended in those liable to severe asthma attacks. Abnormalities in eicosanoid biosynthesis and of eicosanoid receptor expression coupled with mast cell and eosinophilic infiltration of the respiratory tract are involved. Beta-blocker-induced bronchospasm can be abrupt and fatal in minutes to a few hours [198, 199]. This form of catastrophic asthma can be difficult to treat, as ß-blockade may blunt the response to ß2-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 had been fatal [192]. Of interest, the bronchospasm was fatal in five of the six patients with a history of asthma. Novel selective ß-blockers may not induce measurable bronchospasm or asthma and may confer a survival advantage to chronic obstructive pulmonary disease patients, however it is good practice to stay on the safe side with this class of medications.

In the recent past, inhaled/insufflated heroin, cocaine and crack cocaine has coincided with a sizable increase in the rate of severe asthma attacks and of admissions in emergency departments [200–202]. Levine et al. examined 152 patients, 42 cocaine and 47 heroin users [202]. Intubation rate was higher in cocaine and heroin users (21.4 and 17.0 %, respectively) compared to nonusers in whom the rate was 2.3 %. Likewise, Krantz et al. found a 56 % incidence of heroin inhalation in a sequential ICU admission study in 23 patients [203]. At the present time at least in the US and/or in major cities, heroin insufflation is considered a common trigger for acute severe asthma. Screening all adults with asthma who present to the emergency department using the urine drug screen is indicated [203].

A popular test in young people is the ‘Dry Cinnamon Inhalation Challenge’ whereby the subject attempts to inhale a large spoonful of the compound [204]. As not enough saliva is available to humidify and swallow the given amount of

fine cinnamon powder, inhalation, acute bronchospasm may follow inhalation with foreign body related bronchiolitis and ILD developing in the aftermath of the episode.

Peri-operative Emergencies

Few situations cause more distress and carry more risk than acute intraoperative respiratory events, as the time allotted to understand and solve the issues can be extremely short. Many respiratory emergencies are the direct consequence of drugs taken at baseline, or of anesthetic or nonanesthetic drugs given during the surgical or endoscopy procedure: Anaphylaxis (due to anesthetic or contrast agents, neuromuscular blocking agents, latex or antibiotics), UAO from ACEI (see above), explosive coughing from fentanyl, acute severe bronchospasm from anesthetic agents or muscle relaxants, pulmonary edema or ARDS as a complication from narcotics dextran or blood transfusion, plasma or proteins, nonthrombotic pulmonary embolism from aprotinin or methacrylate, protamine-induced acute pulmonary vasoconstriction, fat embolism from propofol, and drug-induced methemoglobinemia [2] and Table 34.6. The above complications have an extra grade of severity intraoperatively and this requires emergent recognition and management.

Patients who are on regular preoperative ACEI can develop pre-, intra- or postoperative acute UAO following the trauma of airway intubation (see above) [205] (Table 34.7).

Drugs taken at baseline can cause acute intraoperative methemoglobinemia [206–209], for instance preoperative exposure to chloroquine, dapsone, metoclopramide, sulfonamide or recreational inhalants (amyl- or isobutyl-nitrite), or intraoperative exposure to benzocaine, lidocaine, nitroglycerine, nitro compounds or nitric oxide may lead to methemoglobin formation a disease of hemoglobin where one-to-four of the four ferrous iron atoms linked to each of the four hemes in hemoglobin is oxidized into the ferric state (Fe+++) [210]. Fully oxidized methemoglobin cannot carry dioxygen. The condition manifests with the progressive or rapid onset of slate-gray cyanosis resistant to high-flow oxygen and chocolate-brown blood color than does not turn red when exposed to oxygen or room air [211, 212]. Significant levels of methemoglobin (25–40 % (Normal <3 %) of total hemoglobin) are associated with low pulse saturation (SpO2) readings (60–70 % range) despite normal or above normal PaO2, depending on FIO2 in the breathing mixture. True hemoglobin saturation needs be measured and not calculated or presumed from PaO2 measurement, otherwise the diagnosis can be missed. A significant saturation gap (Calculated minus measured SaO2) is suggestive of methemoglobinemia. Multi (four) wavelength sensors are appropriate for measuring methemoglobin and carboxyhemoglobin in addition to oxy- and deoxyhemoglobin or SaO2 is measured spectrophotometrically *in vitro*. Methemoglobinemia in excess of 50–60 % can induce arrhythmia, central nervous system symptoms including seizures and coma, metabolic acidosis and figures above 70 % can be fatal. Treatment is with oxygen and the reducing agent methylene blue in the order of 1.5 mg/kg in 5 min, after which disappearance of discoloration, normalization of SpO2 and a drop in methemoglobin should be observed within 1 h [213, 214]. Careful monitoring is required though, as administration of methylene blue can be needed but may cause paradoxical methemoglobin formation. Failure to obtain response may result from ongoing exposure to the culprit drug or chemical, or to a background of NADPH deficiency especially in newborns and infants. Methylene blue availability should be checked preventatively in any hospital as this may be life-saving.

Table 34.7 Catastrophic intra- and perioperative drug-induced and iatrogenic emergencies

Step	Occurrence	Tyoical causal drugs	Risk factor	Management/prevention Stoppage indicated as the first measure in all cases	Major complications
Intubation	Anaphylaxis	Muscle relaxants, cristalloids	Atopy?	Fluid resuscitation, CS, antihistamines, supportive	CV collapse
	Angioedema	ACEI/ARB	ACEI, ARB	O2, 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		O2, MV, naloxone	Hypoxia
	Explosive coughing	Fentanyl	Smoking	Dezocine, pentazocine, propofol	Wound dehiscence

Table 34.7 (continued)

Step	Occurrence	Tyoical causal drugs	Risk factor	Management/prevention Stoppage indicated as the first measure in all cases	Major complications
Intraoperative	Angioedema	ACEI/ARB	ACEI, ARB	See above	Asphyxia Brain death
	Airway fire	Lime + sevoflurane interaction. Laser, cautery	Flamable mixtures	Switch off O2, 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 an 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, nafazoline	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 doxurubicin		Drug stoppage. Supportive care	ARDS
	Acute pulmonary vasoconstiction	Reversal of heparin with protamine		Nitric oxide Drug stoppage. Supportive care	CV collapse Death
	Cement embolism	Acrylate	Leakage from vertebral body	Drug stoppage. Supportive care	CV collapse, death
	Oxygen toxicity	O2	Prior exposure to chemo agents	Monitor for lowest possible FIO2	ARDS
	Methemoglobinemia	Benzocaine, dapsone and other		O2. Consider methylene blue. Ensure methylene blue availability	Pulmonary edema Hypoxic brain death
Postoperative, early	NPPE	–	Central airway or tubing 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	O2	Monitor for lowest possible FIO2	ARDS
Postoperative, late	ILD/IPF exacerbation	Amiodarone, bleomycin	High intraoperative FIO2	Monitor for lowest possible intrraoperative FIO2	ARDS
	Worse outcomes in general	Blood		Restrictive transfusion policy	

An important and often overlooked area is the pulmonary toxicity of molecular oxygen. In particular, elevated and FIO2 on a previously drug- or radiation-exposed lung for even a short period of surgery may be damaging. Undeniable acute postoperative deterioration of ILD and ARDS has been reported in patients previously exposed to amiodarone, bleomycin, chemotherapeutic drugs and radiation who did not have preoperative evidence for ILD [215–217]. 'Whitening' of the single lung that has been ventilated using 100 % oxygen during surgical procedure is consistent with this view [144]. At any rate, keeping intraoperative FIO2 as needed to ensure an adequate SaO2 is indicated in any patient who

has a history of exposure to pneumotoxic drugs, particularly amiodarone, bleomycin, nitrosoureas, chemotherapeutic agents at large or radiation.

Cases of negative pressure pulmonary edema (NPPE) have increased since the 1980s [218, 219]. This form of pulmonary edema appears to be related to the barotrauma of forceful inspirations against a closed airway. Markedly negative swings of intrathoracic pressure can cause exit of fluid or blood from damaged or fractured pulmonary capillaries toward the interstitium and alveolar spaces [220]. Causes of airway closure have included biting or obstruction of the endotracheal or laryngeal tube, goiter, trauma, amygdalitis, oropharyngeal surgery, tonsillectomy, vocal cord adduction, postanesthetic laryngospasm, laryngeal edema, septoplasty, foreign body inhalation and any type of rapid-onset upper-airway obstruction including rheumatoid arthritis-associated airway closure or ACEI-induced upper airway obstruction [221, 222]. Diagnosis is suggested by the sudden onset of dyspnea and hypoxemia in the appropriate, often postoperative clinical setting, accompanied by bilateral batwing pulmonary opacities. Severe cases are complicated by full-blown pulmonary edema, froth at the mouth, and/or diffuse alveolar hemorrhage [223]. 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 at all times.

Unusual Presentations

Pulmonary Nodules and Masses

Pulmonary reactions to eighteen discreet drugs or radiation can be in the form of a pulmonary a nodule, nodules or a mass [2]. The main differential is malignancy or an infection. Nodules with ill-defined borders are a classic complication or chest radiation therapy, particularly with the novel stereotactic body radiation therapy technique where gantry rotates around the patient's body [224, 225]. Areas of radiation-induced lung injury may assume a whorled or convoluted appearance are densest in the area with the greatest amount of radiation. Uptake values on PET scan tend to decrease with time, as opposed to recurrence of the underlying malignancy [224].

A solitary lung nodule or a mass is a classic manifestation of mineral oil aspiration and the name paraffinoma is appropriate, although a bilateral more diffuse pattern of involvement is more common. Paraffinoma may simulate malignancy and be tracer-avid on PET scan [226].

Multiple nodules can develop in children or in adults during or following therapy with carbamazepine, minocycline, hydralazine or antineoplastic agents notably bleomycin [2]. The main issue is eliminating disease progression. Review of pretherapy chest imaging, response of the underlying disease to treatment, PET scanography, watchful follow-up or the lung biopsy are indicated. Nonneoplastic nodules, when examined on pathology, corresponded to organizing and/or eosinophilic pneumonia [2].

Several disease-modifying antirheumatic drugs (DMARDs) including methotrexate, leflunomide and anti-TNF agents have been temporally associated with the development or progression of pulmonary nodules (pulmonary nodulosis) mainly but not exclusively in rheumatoid arthritis [2, 227, 228]. Nodules can be moderately tracer-avid on PET-scan examination. The main issues are eliminating an infection and tuberculosis, particularly in those patients exposed to anti-TNF drugs and malignancy as rheumatoid arthritis is more prevalent in smokers. Drug discontinuation, maintenance of therapy with the DMARD, or rituximab have met with some success. The causal role of drugs is unclear as this time.

Amiodarone pulmonary toxicity may manifest with multiple round-shaped opacities, a mass or masses in about 10 % of the cases. Large masses are coined amiodaronoma [2]. Nodules or masses have ill-defined, indistinct borders and can be surrounded by a halo of decreasing attenuation peripherally [229]. Nodules can be deep-seated in the lung, or are noted peripherally abutting the pleura causing localized pleural thickening and/or pleuritic chest pain. Some nodules are discovered incidentally on CT. They may exhibit high CT numbers due to the iodinated chemistry of amiodarone [230]. On pathology, nodular APT shows the classic features of APT including chronic interstitial inflammation, myofibroblasts, organizing pneumonia and foam cells, which are decreasing peripherally. Other patients present which one or more rounded or dented masses up several centimeters in their larger dimension [2, 231]. There may be decreased attenuation in the center of the mass suggesting aseptic necrosis. Ruangchira-Urai et al. described the pathologic features of four such nodular APT cases [231]. Three of the four cases 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 excision was indicated with the suspicion of malignancy. The PET-scan was positive in the single case so tested. Histopathology in all four patients showed "vacuolated histiocytes massed within alveoli to form macroscopic nodules with tissue breakdown", smudged geographic necrosis and purulent abscess [231]. On electron microscopy, the char-

acteristic cytoplasmic inclusions were present in histiocytes and macrophages. Keeping in mind this unusual, yet distinctive APT presentation may obviate the need for resectional lung biopsy. Also, the drug history should be given to the pathologist, as the drug history of none the four cases by Ruangchira-Urai was available to the pathologist at the time of examination [231].

Pleuroparenchymal Fibroelastosis

This distinctive syndrome has been better delineated in the past few years [232–234]. Clinical presentation is with dyspnea, markedly restrictive physiology, biapical pleural thickening on imaging, and often is 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 [232, 233] and there is abrupt transition to a normal architecture in the deeper lung undeerneath the pleura. Although most such cases are deemed to be idiopathic, a few were exposed to chemotherapeutic agents notably cyclophosphamide [235] or are recipients of stem cell or lung transplant [232, 233, 236].

Late Radiation-Induced Injury

Beside classic radiation-induced pneumonitis, a subset of atypical distressing, sometimes devastating radiation-induced injuries to the chest, heart, mediastinum and neck. Clinical presentations include painful myositis of intercostal muscles, constrictive pericarditis, coronary- or valvular heart disease, fibrosing mediastinatis, bilateral phenic nerve palsy, chronic compressive pleuroperiocardial effusion or thickening, neck musculature problem and the 'dropped-head syndrome' or swallowing disorders leading to food aspiration and debilitating aspiration pneumonia. Many of these patients are considered saved when these difficult-to-treat late complications of treatment developed [237].

Chest Pain

Drug induced acute transfixiating chest pain can be a cause for emergency admission [2]. The condition results from drug-induced pleuritis, subpleural pulmonary involvement, acute coronary artery disease, pulmonary vasoconstriction, pericarditis or it is associated with no clinically demonstrable disease. Drug-induced acute chest pain has been reported with the use of nitrofurantoin, methotrexate, high-dose methotrexate, lupus-inducing drugs including beta-blockers, interferons, carbamazepine, hydralazine, sulfasalazine, mesalazine, bleomycin, 5-fluorouracil, vindesine, adenosine 5′-triphosphate, triptans, cocaine, and crack cocaine [2]. Failure to identify the drug etiology exposes to the risk of distressing relapses and readmissions. Acute transient chest pain has also been reported following sclerotherapy of oesophageal varices, arteriovenous closure of brain arteriovenous malformations and kyphoplasty [2].

Rebound Phenomenon

Rebound consists in a life-threatening flare of the underlying disease that occurs upon withdrawal of a therapy drug. Examples include rebound pulmonary hypertension upon cessation of prostacyclin or nitric oxide, relapse or amiodarone pulmonary toxicity or DRESS or the development of acute radiation pneumonitis after removal of corticosteroid therapy, early relapse of ACEI-associated angioedema or of methemoglobinemia after removal of specific therapy or antidote, recurrence of the clinical manifestations of opioid toxicity following termination of naloxone, and the ruxolitinib withdrawal syndrome [4, 238–243].

Recall Phenomenon

Recall is the flare that may follow the administration of small amounts of a drug or agent in a patient with a history of exposure to pneumotoxic drugs or radiation [244]. Recall pneumonitis developing after chemotherapy in the previously irradiated field in patients with a history of irradiation to the chest typifies recall pneumonitis. Similar examples include ARDS triggered by oxygen in patients previously exposed to amiodarone.

Thoracic Bezoars and Gossypibomas

Bezoars and pharmacobezors are aggregates of food or other foreign material or drugs. They may localize in the chest, obstructing the central airway or esophagus [245]. Pharmacobezoars including body packing may act as a slow release drug reservoir capable of perpetuating the adverse effects from a drug [246, 247].

Postoperative leftover of surgical sponge, fabric or catheters may lead to gossypiboma or textiloma. These may have distinctive HRCT features [248] and may simulate primary chest malignancy [249, 250].

Respiratory Diseases Considered Idiopathic that May Be Drug-Induced (Table 34.8)

A number of common diseases including ILD as cellular NSIP, organizing pneumonia, pulmonary alveolar proteinosis, pulmonary fibrosis, exacerbated pulmonary fibrosis, sarcoidosis, hilar or mediastinal lymphadenopathy or ILD with a granulomatous component, pulmonary edema, ARDS, diffuse alveolar hemorrhage, angioedema, deterioration of asthma, chronic cough, pleural effusion including chylothorax, pulmonary embolism, emphysema, disordered breathing during sleep, hiccup, such systemic syndromes as *lupus*, drug rash with eosinophilia and systemic symptoms, ANCA-related vasculitis, eosinophilic granulomatosis and polyangiitis, polymyositis), the multiple organ dysfunction syndrome, or cardiomyopathy can be triggered or caused by exposure to drugs [2]. Consideration of the drug condition in such conditions can be rewarding in terms of reversal of all signs and symptoms with drug removal.

Drug-Induced Respiratory Disease in Nonpulmonary Disciplines

A wealth or DIRD can be admitted to or evaluated in nonpulmonary wards (Table 34.9). Knowledge-sharing of this pathology with colleagues is indicated for the purpose of early recognition, diagnosis and management. A detailed list is available in Table 34.9. Many of these conditions are amenable to preventive measures.

Lung transplant (single, or bilateral) recipients can develop parenchymal complications in the transplanted lung that appear to be related to drugs. Drugs account for

Table 34.8 Lung diseases with a significant background rate for 'idiopathic' that may be drug-induced

	% drug-induced	Established or suspected causal drugs or agents
NSIP-cellular ILD	3 %	Nitrofurantoin, methotrexate
ILD with a granulomatous component		Interferon, BCG-therapy, anti-TNF antibody therapy
Organizing pneumonia	20–30 %	Nitrofurantoin, amiodarone, statins, interferons
Pulmonary fibrosis		Nitrofurantoin, chemotherapy, radiation therapy
Exacerbated pulmonary fibrosis		Amiodarone, antineoplastic chemotherapy, TKI, anti-TNF agents
Accelerated pulmonary fibrosis (AIP)		Anti-TNF agents
Sarcoidosis		Interferons
Hilar or mediastinal lymphadenopathy		Interferons
Pulmonary alveolar proteinosis		Busulfan, imatinib, sirolimus
Pulmonary edema		Tocolytics, salicylate, hydrochlorothiazide, chemotherapy agents
ALI/ARDS	10 %	Amiodarone, chemotherapy agents
Diffuse alveolar hemorrhage	10–20 %	Anticoagulants, platelet aggregation inhibitors, propythiouracil, cocaine-levamisole
Angioedema	35 %	ACEI, ARB
Deterioration of asthma		Beta-blockers (topical)
Chronic cough		ACEI + others
Pleural effusion incl. chylothorax		Amiodarone, dantrolene, imatinib, dasatinib, ergots, glitazones, irradiation
Pulmonary embolism		Darpoetin alpha, lenalidomide, thalidomide, neuroleptic agents
Disordered breathing during sleep		ACEI, opiates
Hiccup		Chemotherapy drugs
Lupus and serositis	10 %	Anticonvulsants, beta-blockers
DRESS		Anticonvulsants, minocycline
ANCA-related DAH/vasculitis	High if dual ANCA or polyspecific ANCA	PTU, cocaine-levamisole
Eosinophilic granulomatosis with polyangiitis		LTRA, omalizumab
Polymyositis		Statins
Pulmonary aspergillosis		Marijuana
Cardiomyopathy		Chemotherapy drugs, cocaine, imatinib, glitazones

Full list of causal drugs per syndrome available in Pneumotox
Drug therapy withdrawal (dechallenge) indicated. Follow-up may show improvement in drug-induced cases
Blank: no data available

about 2 % of all interstitial lung disease in that setting [251]. Diagnostic issues are complicated as considerations include rejection and an infection. Cyclosporine (anaphylaxis), tacrolimus (ILD reported in Japan), sirolimus with NSIP-like disease, ILD with granulomas, DAH, OP, and pulmonary alveolar proteinosis or vasculitis have been described and a class effect is likely to be shared with other inhibitors of the m-TOR pathway [2].

Patients with a history of pneumonectomy are not immune to the development of drug-induced ILD. Cases of nitrosourea-, amiodarone-, and radiation-induced ILD have also been reported in this setting [141].

Table 34.9 Drug-induced respiratory diseases in nonpulmonary disciplines

Setting – Specialty	Clinical pattern of involvement	Causal drugs or conditions (full list on Pneumotox.com)
Family practice	Acute pneumonitis & chest pain	Nitrofurantoin
	Chronic ILD/fibrosis	Nitrofurantoin
	Chronic cough, angioedema	ACEI
	Subacute pneumonitis	Amiodarone (annual CXR indicated in the amiodarone-trreated patient)
Emergency Department ICU	Angioedema and difficult to intubate UAO	ACEI (ARB)
	Acute asthma attack	ß-blockers, NSAIDs
	Anaphylaxis (Shock, collapse, acute airway obstruction)	Antibiotics, NSAIDs, oxaliplatin, biologics and many other drugs
	Diffuse white out and respiratory failure, ALI/ARDS	Drugs which cause NCPE, ARDS, DAH, ILD, PIE, BOOP, salicylate, heroin, paraquat
	TRALI	Transfusion of blood or components
	Diffuse alveolar hemorrhage (DAH)	Anticoagulants, anti-platelet aggregating agents, marijuana, cocaine, brodifacoum
	Hemothorax	Oral anticoagulants
	Skin necrosis w/wo DAH	Cocaine-levamisole poisoning
	Airway burns	Crack cocaine
Anesthesia	Neuromuscular failure, apnea	Curares, opiates, polymyxin
	Anaphylaxis	Antibiotics, dextran, dyes, latex, muscle relaxants, propofol
	NCPE	Propofol, opiates, adrenaline
	Acute explosive coughing	Fentanyl
	Unexplained cyanosis and low Sp readings (methemoglobinemia)	Topical anesthetics, oxidizing agent, dapsone
Postop care	Negative pressure pulmonary edema	Compromised airway
Endoscopy suite	Unexplained cyanosis (methemoglobinemia) and low SpO2 readings	Topical anesthetics
	Airway fire	Foreign material, oxygen, sevoflurane
Oncology: solid tumors	ARDS (NCPE, DAD, DAH, acute ILD)	Chemo agents including novel TKI (gefitinib, erlotinib, cetuximab)
	Anaphylaxis	Oxaliplatin, platinum, propofol, other chemo agents
	ILD, BOOP, DAH	Cyclophosphamide, m-TOR inhibitors
	Pulmonary infiltrates, NCPE	G-GM-CSF
	TRALI	Blood and fractions
Renal cell carcinoma care	ILD, OP, DAH	mTOR inhibitors, sunitinib
Hematologic malignancies	NCPE, DAD, DAH	Chemo agents including TKIs and imatinib, ATRA, As2O3
	TRALI	Transfusion of blood or components thereof
	Anaphylaxis	Chemo agents
	ATRA syndrome	ATRA
	ILD	Imatinib, dasatinib, methotrexate
	Pleural effusion, chylothorax	Dasatinib
	ILD	Thalidomide, lenalidomide, pomalidomide, bortezomib
	Longterm respiratory dysfuntion	Chemo agents, radiation therapy

(continued)

Table 34.9 (continued)

Setting – Specialty	Clinical pattern of involvement	Causal drugs or conditions (full list on Pneumotox.com)
Internal medicine	DAH	Anticoagulants, propythiouracil, antithyroid drugs
	ANA-related disease (*lupus*)	*Lupus*-inducing drugs
	ANCA-related disease	PTU, cocaine-levamisole
	PAN	Minocycline
	Pneumorenal syndrome	Cocaine, hydralazine, propythiouracil, antithyroid drugs
	Sarcoidosis	Interferons
Allergy	Anaphylaxis	Omalizumab
	Churg-Strauss syndrome	LTRA
Nephrology	ANCA-related glomerulonephritis	PTU, cocaine, minocycline, cocaine-levamisole
	Diffuse pulmonary calcification	Hemodialysis
Rheumatology	Anaphylaxis	Biologics
	Acute methotrexate pneumonitis	Methotrexate
	Subacute ILD	Leflunomide
	Acceletrated ILD	Anti-TNF agents
	Autoimmune phenomena	Anti-TNF agents
	Pulmonary/systemic infections incl. tuberculosis an *Pneumocystis* pneumonia	Corticosteroids, anti-TNF agents
Cardiology	Insidious or acute ILD	Amiodarone, statins
	Acute bronchospasm	ß-receptor blockers
	Chronic cough	ACEI
	Serositis	*Lupus*-inducing drugs
	DAH	Any platelet aggregation inhibitor
Infectious disease	Pulmonary/systemic infections incl. tuberculosis an *Pneumocystis* pneumonia	Corticosteroids, anti-TNF agents
	Immune reconstitution syndrome	Highly active antiretroviral therapy for AIDS
	Acute eosinophilic pneumonia	Malaria prophylaxis, minocycline
Post-lung Tx status	ILD	Sirolimus
Post-pneumonectomy status	ARF	Any drug causing ILD or bronchospasm
PHTn clinic	Bleeding	Anticoagulants
	Rebound PHT	Unexpected withrawal of pulmonary vasodilator drugs (prostacyclin, NO)
	NCPE	Vasodilator drugs
	NCPE	Nitric oxide NO
Ob-Gyn	NCPE	Tocolytic ß2 agonists
	Dextran syndrome	Dextran
Pediatrics	Acute ILD	Methotrexate
	Subacute-chronic ILD	Chemotherapy, conditioning, amiodarone, stem cell Tx
	NCPE	Blood transfusion, chemo agents, methotrexate
	Pulmonary fibrosis	Nitrosoureas, busulfan
	Late restrictive physiolgy	Chemo agents, radiation therapy
Dermatology	Pulmonary infiltrates and eosinophilia	Minocycline
	DRESS (rash, eosinophilia, deep-organ involvement)	Anticonvulsants, minocycline
	Necrotizing vasculopatrhy	Cocaine-levamisole
	Acute ILD	Acitretin
	Methemoglobinemia	Dapsone
Endocrinology	DAH, pneumorenal syndrome	Propylthiouracil, antithyroid drugs
Neurology	DRESS	Anticonvulsants
	Pleural effusion or thickening	Ergots
Gerontology	Lipoid pneumonia	Paraffin
Cosmetic surgery	Fat embolism syndrome	Liposuction
	Silicone embolism syndrome	Augmentation therapy
	Hyaluronate embolism	Cosmetic/plastic surgery

Abbreviations: see text

Conclusion

Drug-induced respiratory problems are manifold and can be immediately life-threatening. Many are rare. Prevention rests on a high index of suspicion, examining almost any constellation of signs and symptoms for their possible drug-relatedness using Pneumotox and the literature, avoidance of combined treatments with agents that mutually potentiate each other's toxicity, prompt identification of the causal agent and its removal, and reliable measures to avoid rechallenge with the culprit drug.

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From Cancer Mimicking Orphan Lung Disease to Orphan Thoracic Oncology

35

Nicolas Girard, Vincent Cottin, and Jean-François Cordier

Lung cancer is by far the most frequent intra-thoracic cancer, and is the first cause of cancer-related mortality worldwide [1]. It is then the first diagnosis to consider when facing a tumor lesion involving the lung, the pleura, and/or the mediastinum, especially in smokers [2]. However, physicians may be aware of rarer neoplastic and non-neoplastic disorders that may have a propensity to mimic lung cancer at some level of examination [1–6]. Furthermore, several rare intrathoracic tumors are associated with a peculiar phenotype, as such entities may share some of the clinical, radiological, pathological, and even molecular features of non-neoplastic orphan lung diseases. Numerous disorders may be considered, but the challenges in the differential diagnosis is well illustrated through the examples of bronchioloalveolar carcinoma, as well as primary pulmonary lymphomas and vascular sarcomas.

Pseudotumors have further been described in the thorax, historically referring as to any pseudoneoplasm, but currently restricted to a specific heterogeneous group of diseases characterised by a circumscribed fibrous tissue associated with inflammatory and myofibroblastic cells [4, 6]. Among those, neoplastic/non-neoplastic borderline disorders have been identified, such as inflammatory myofibroblastic tumor with clonal proliferation, thus emerging as a true neoplasm [7, 8].

Other rare pulmonary disorders are emerging as borderline neoplastic-non-neoplastic disorders, 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 imaging including 18-fluoro-desoxyglucose positron emission tomography (18-FDG-PET) scans, the request of specific molecular analyses on often small-size biopsies, and ultimately a dedicated multi-disciplinary expert consensus.

Cancer Mimicking Orphan Lung Disease

Cancer Mimics of Organising Pneumonia

Organising pneumonia is a classical diagnostic pitfall for lung cancer, as it may occasionally present as a solitary mass-like lesion, leading to conduct unnecessary diagnostic procedures and even surgical resection, especially in smokers [9]. The landmark feature of this condition consists of intra-alveolar fibroblast and myofibroblast, connective matrix organisation that fills the alveolar spaces, the alveolar ducts, and the respiratory bronchioles. In patients treated for malignancies, cytotoxic drugs may induce organising pneumonia; although usually not presenting as focal lesion, organising pneumonia may mimic multiple pulmonary metastases. This has especially been reported with bleomycin treatment for germ-cell testicular cancer, embryonal tumors, and Hodgkin lymphoma [10].

The organising pneumonia imaging pattern is shared with some lung cancers, including bronchioloalveolar carcinoma

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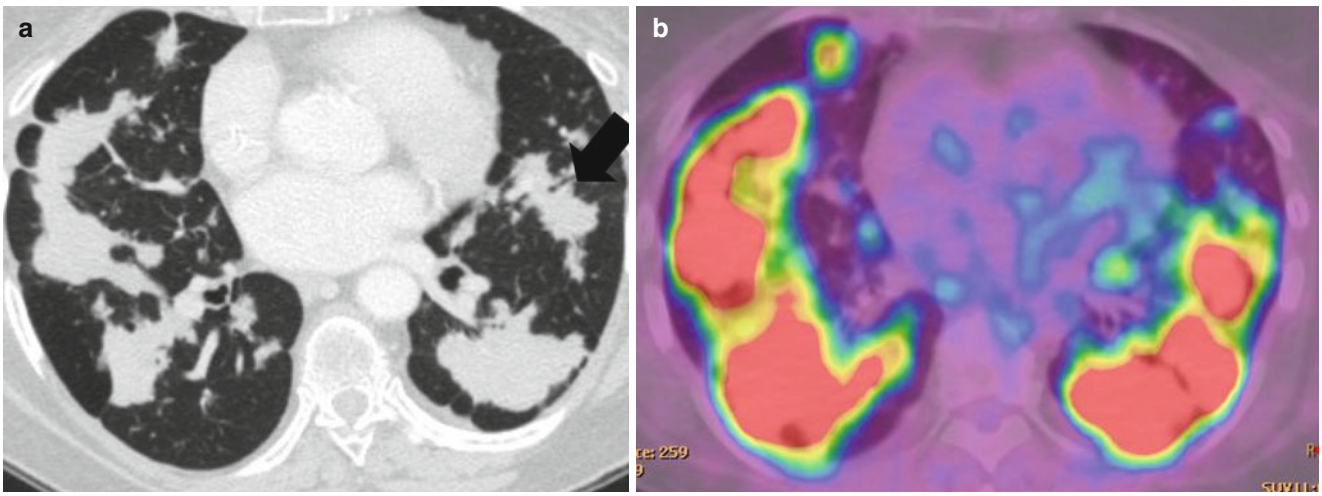

Fig. 35.1 Pneumonic-type lung adenocarcinoma. (**a**) Computed tomography scan of a 66 year-old former smoker woman, who presented with progressive cough. Multiple bilateral alveolar condensation-like masses with irregular margins are observed, some of which with air bronchogram. (**b**) 18-fluoro-desoxy-glucose positron emission tomography scan shows hypermetabolism of all the lesions. Transparietal biopsy showed adenocarcinoma cells with bronchioloalveolar and papillary architecture. No *EGFR* mutation was detected. The patient received platinum-based chemotherapy

and primary pulmonary lymphoma, that are characterised by tumor cell spread in the alveolar spaces, leading to a common radiological pattern of alveolar opacities with air-bronchogram [6].

Bronchioloalveolar Carcinoma

Bronchioloalveolar carcinoma has extensively been described elsewhere [11, 12]. It has actually been a term referring to several clinical-radiological-pathological entities of lung adenocarcinoma, which share a variable degree of 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: (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 organising pneumonia. Other major differential diagnoses of bronchioloalveolar carcinoma include infectious opacities, and MALT lymphoma. The recent consensus about lung adenocarcinoma classification proposes to actually delete the term "bronchioloalveolar carcinoma" from the nomenclature to avoid historical misunderstanding [12].

Adenocarcinoma in situ, formerly known as pure bronchioloalveolar carcinoma, usually presents as a localised coin-like lesion, less of 3 cm in size, showing predominant ground-glass pattern usually surrounding a solid lesion, possibly with air-bronchogram, and located at the periphery of the lung parenchyma [12]. Papillary or micropapillary features and intraalveolar tumor cells are absent. Cells are usually nonmucinous and originate from type II pneumocytes and/or Clara cells of the terminal respiratory unit [11]. Molecularly, these tumors frequently harbour Epidermal Growth Factor Receptor (*EGFR*) mutations; *KRAS* mutations are frequently found in case of mucinous pattern [12]. These tumors may preferentially develop in non-smokers. Patients are usually asymptomatic. The lesion may show normal metabolic activity at FDG-PET [13]. Given the localised 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 synchronous and metachronous independent tumors.

Pneumonic-type lung adenocarcinoma (PTLA) is a clinical-radiological-pathological entity that is not strictly defined in the histopathologic adenocarcinoma classification [14]. 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 characterised by little or no loss of volume, disappearance of blood vessel shadows and, sometimes, and the presence of an air bronchogram (Fig. 35.1) 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

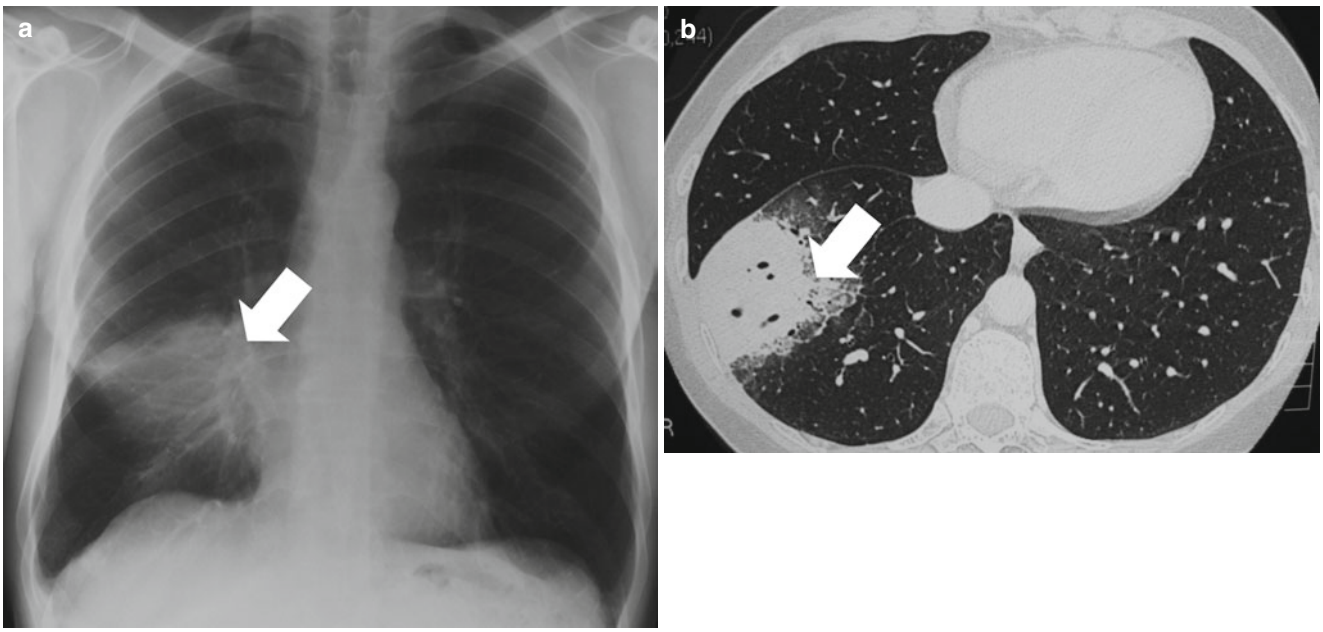

Fig. 35.2 Pulmonary primary MALT lymphoma in a 56 year-old man. (**a**, **b**) Chest radiography and computed tomography scan show persistent alveolar opacities in the right lower lobe (*arrows*), despite prolonged antibiotic therapy. Pathological examination of surgical biopsy showed lymphoplasmacytic-like cells of the marginal zone lymphoma associated with amyloid deposit. The patient received treatment with chlorambucil, that led to complete regression of the lesion

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 [14]. The epidemiology of PTLA differs from that of other non-small cell lung cancers, with less important epidemiologic link 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 localised lesions and chemotherapy for disseminated tumors; the role for limited surgical resection is debated. Chemosensitivity is actually limited given the slow growing pattern. In the absence of *EGFR* mutation, chemotherapy may consist of the combination of paraplatin and paclitaxel, possibly combined with bevacizumab [15].

Primary Pulmonary Lymphoma

Primary pulmonary lymphoma is defined as a lymphoma affecting one or both lungs, without evidence of extrapulmonary involvement or bone marrow disease at the time of diagnosis [16–18]. Primary pulmonary lymphomas are rare, representing 0.4 % of all lymphomas. Most frequent subtype is Mucosa-Associated Lymphoid Tissue (MALT) lymphoma, which is more frequently observed in patients older than 45 years, with a slight male predominance; it may also arise in younger patients with underlying immunosuppressing condition, and in patients with Gougerot-Sjögren syndrome. Less than 50 % of patients are symptomatic, with nonspecific symptoms, including cough, dyspnea, and chest pain. Unlike other lymphomas, systemic signs, such as fever, swelling, and weight loss, are uncommon. Association with immunoglobulin (Ig)M or IgG blood monoclonal gammopathy, with or without monoclonal Ig light chain secretion, possibly resulting in amyloidosis or non-amyloid monoclonal immunoglobulinic deposition disease, is observed in 30 % of cases, and may reveal the disease.

The most frequent and suggestive imaging aspect of MALT lymphoma is the "pneumonia- like" alveolar consolidation with an air bronchogram, typically localised in the middle lobe (Fig. 35.2). The "tumor-like" aspect with a solitary well-circumscribed nodular opacity is observed in 30 % of cases, with possible central air bronchogram. The "infiltrative" pattern with diffuse poorly defined ground-glass opacities, is far much rarer and may mimic, besides organising pneumonia, infiltrative lung disease and is assumed to represent early-stage disease before tumor cells invade alveolar spaces. The combination of a nodular opacity with peripheral peribronchovascular ground-glass attenuation halo is frequent. When present, associated moderate pleural effusion is suggestive of the diagnosis. FDG-PET scan may not be sensitive enough in MALT lymphoma, especially to exclude extrathoracic disease [18].

The diagnosis often requires a surgical lung biopsy, as cytological examination of bronchoalveolar lavage or fine-needle biopsy may show the CD20-positive B-cell infiltration but fails to exclude differential diagnoses, such as reactional lymphoid proliferation, follicular bronchiolitis, or

lymphoid interstitial pneumonia [17]. Pathologically, MALT lymphoma appears as a diffuse infiltrate of small monomorphic lymphoid cells and plasmocytes, 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 is 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. The proliferation is monotypic, with surface and/or cytoplasmic expression of immunoglobulin M (IgM) 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 (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, but more specific to lung locations -, and the t(14;18)(q32;q21) involving the *BCL-2* and *MALT1* genes [19]. These translocations may be identified in bronchioloalveolar lavage or pleural fluid specimens. In contrast with gastric and ocular annexae MALT lymphomas, no chronic infectious condition has been associated with pulmonary MALT lymphoma, although concurrent evolution with chronic hepatitis C has been described.

Therapeutic options are based on the degree of tumor extension. Surgical resection ensures both the diagnosis and the treatment of solitary nodular lesions. In asymptomatic patients, a watch-and-wait attitude may be preferred. More advanced MALT lymphoma requires more aggressive management, including single-agent chemotherapy with chlorambucil, fludarabine, and/or rituximab. Rituximab, an anti-CD20 antibody, is particularly effective and well-tolerated and may represent an alternative to chemotherapy, especially in case of t(11;18) translocation. The prognosis of MALT lymphomas is excellent, with an indolent and localised prolonged course. Local and systemic recurrences may develop in about 50 % of patients, but are usually controlled with chemotherapy. Evolution to high-grade B-cell lymphoma occurs in less than 5 % of cases.

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 hemangio-endothelioma and lymphomatoid granulomatosis.

Lymphangitic Carcinomatosis

Pulmonary lymphangitis carcinomatosis is a metastatic lung disease characterised by the diffuse infiltration and obstruction of the pulmonary parenchymal system by tumor cells [20]. Pulmonary lymphangitis carcinomatosis accounts for up to 10 % of all thoracic metastases. Patients are usually diagnosed in their fifth decade. Dyspnea is usually the chief symptom [21]. 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 ressembles Kerley B lines, (2) a more limited or diffuse peripheral interlobular septa thickening producing polygonal arcades, and/or (3) a more aspect referred to as "beaded chain" or "string of pearls" thickening of interlobular septa [22]. These features may be diffuse or localised, uni- or bilateral, and symmetric or not. Micronodules may be observed within the thickened septa. Rapidly progressive asymmetric lymph nodes are 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 granulomatosis, originating from the following primary anatomic locations: breast (33 %), stomach (29 %), lung (15 %), pancreas (4 %), and prostate (3 %) [23]. Survival is usually poor, ranging from 3 to 6 months [21–23].

Differential diagnosis includes other infiltrative lung diseases, sarcoidosis, as well as bacterial or fungal infections, such as pneumocytosis, especially in case of treatment with cytotoxic agents in patients otherwise treated for cancer [24]. Bronchoalveolar lavage is the key to make these diagnoses. Lymphangitic carcinomatosis may also be confused with drug-induced interstitial lung disease especially in patients receiving chemotherapy or biotherapy; imaging patterns may include ground-glass opacities and interlobular septa thickening. Multiple causes of interstitial lung disease may actually be interlinked in cancer patients.

Epithelioid Hemangio-Endothelioma

Epithelioid Hemangio-Endothelioma (EHE) is a low- to intermediate-grade mixed epithelioid, endothelial, and vascular tumor [25, 26]. EHE is primarily located in the liver in 65 % of patients, and the lungs are the most frequent extrahepatic location (10 % of cases); other locations include the skin and the bone [26]. EHE was initially considered an intravascular and intra-alveolar extension of bronchoalveolar carcinoma, and thus was called "intravascular bronchoalveolar tumor". However, now it is clearly identified as a mesenchymal tumor, corresponding to low-grade angiosar-

coma. Clinically, 80 % of cases of EHE occur in white females. Median age ranges from 35 to 50 years. The tumor is asymptomatic in 50 % of cases; when present, symptoms are nonspecific and include pleuritic chest pain, nonproductive cough, dyspnea, and haemoptysis [27]. Physical examination may reveal inspiratory crackles in 30 % of cases.

At imaging, EHE appears either with bilateral slow growing perivascular multiple nodules, usually located close to small vessels or bronchi, or with predominant infiltrative ground-glass opacities, with a micronodular pattern, mimicking lymphangitic carcinomatosis or infiltrative lung disease. EHE nodules usually range from 3 to 50 mm, and their number varies from 10 to 20 lesions. Nodules show increased uptake at FDG-PET scan. Nodules rarely present with cavitation or cystic features. The diagnosis may be done on either tumor lesion.

Histologically, EHE is characterised by polypoid nodules, with a central sclerotic paucicellular zone, growing into the alveolar spaces with an angiocentric distribution. Lymphangitic spread may mimic metastatic adenocarcinoma, as well as infiltrative lung diseases. Detection of the translocation t(1;3)(p36.3;q25) involving the *PAX7* gene may be helpful to make the diagnosis [28]. EBV RNA sequences are detected in 90 % of cases. Overlapping entities with IgG4-related disease have been described (see below).

Although there are a few reports of spontaneous remission, the complete resection of all pulmonary nodules is the only known curative treatment of EHE. Surgery remains effective even in cases of localised recurrence. In contrast, EHE is generally insensitive to chemotherapy (cisplatin-based) or radiotherapy. Treatments with rituximab or anti-angiogenic kinase inhibitors such as sorafenib, have been reported to be effective in a few case reports [29]. In most cases, EHE is a slow-growing tumor that rarely metastasises and is associated with a median survival of 5–6 years.

The high-grade counterpart of EHE is angiosarcoma, including Kaposi's sarcoma. No direct transformation from EHE to angiosarcoma has been reported. Clinical features are similar to EHE, but massive haemoptysis is more frequent. Radiologic features include multiple nodules with a typical surrounding halo of ground-glass attenuation, with a specific "cauliflower-like" appearance on T2-weighted magnetic resonance imaging [27]. This aspect may be shared by other disorders, including malignancies – bronchioloalveolar carcinoma, metastatic sarcomas, choriocarcinoma, melanoma, lymphoma -, infectious diseases – mycobacteriosis, aspergillosis, cytomegalovirus infection -, granulomatosis with polyangitis, and eosinophilic conditions. Management of angiosarcoma is not established: surgical resection is rarely possible owing to local and regional invasion; radiotherapy and anthracyclin-based chemotherapy is poorly effective. Modulation of immunosuppression in patients receiving immunosuppressive drugs may lead to Kaposi sarcoma remission.

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis, also called "angiocentric lymphoma," is a malignant B-cell angiocentric and angiodestructive lymphoproliferative disorder [30]. Long considered an inflammatory granulomatous disease owing to its radio-clinical presentation that may be similar to other granulomatoses such as granulomatosis with polyangiitis (formerly Wegener's disease) and eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome), lymphomatoid granulomatosis is now recognised 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 [30, 31]. Lymphomatoid granulomatosis occurs in middle-aged patients, from 40 to 50 years old, with a male predominance. Nearly all patients present with respiratory and systemic symptoms, consisting of cough, dyspnea, haemoptysis, chest pain, fever, and weight loss. Prolonged immunosuppression, especially in case of Human Immunodeficiency Virus infection, 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, exhibiting a peribronchovascular pattern, ranging from 2 to 10 cm, and mainly localised in the lower lobes, mimicking multiple metastases [30, 31]. Ground-glass infiltrates may be present. Peripheral and mediastinal lymphadenopathy is absent. As in other granulomatoses, convergent nodules may migrate and form cavitated pseudotumoral masses. Pulmonary biopsy is required in most cases to make the diagnosis.

Pathologically, lymphomatoid granulomatosis 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 characterised mostly as CD4+ T-lymphocytes, with scattered atypical cells of B-phenotype. Large B-cells are infected by EBV in 65 % of cases, a fact that correlates with the grade of the lesion.

Chemotherapy based on high dose-steroids with cyclophosphamide is the most frequently reported treatment of lymphomatoid granulomatosis. The additional use of rituximab may increase the efficacy of these cytotoxic agents [32]. However, the overall prognosis is poor, with a 5-year survival of 30–40 %, owing to progression to nodal diffuse aggressive lymphoma in 20–50 % of patients. 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 benefiting from early aggressive treatment [33].

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 [34]. 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.

Metastastic cancers of extra-pulmonary origin may mimic, when metastasing to the lung, MCLD, especially soft-tissue sarcomas – angiosarcomas [35, 36], leiomyosarcomas [37], osteosarcomas, and synovial sarcoma [37]. Primary tumor location included soft tissues, bones, the scalp or the uterine endometer [38]. 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 poorer outcome [35]. Metastatic cysts may be associated with small-size nodules. In cases for which the information is available, pathological examination showed tumor cells in the wall of the cysts. Several observations were reported, that describe patients for whom metastatic sarcoma was ultimately diagnosed on lung biopsies, or even explanted lungs, after an initial diagnosis of lymphangioleiomyomatosis or pulmonary Langerhans' cells histiocytosis [39].

Besides 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, consolidation area 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; the tumor is then usually unique in the lung parenchyma, and is not associated with extra-pulmonary manifestations in the head and neck area, the skin, the joints or the kidney [40]. Serum proteinase 3-specific, cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA) are not elevated in patients with cancer. Granulomatosis with polyangiitis rarely present with a solitary lung lesion, but most solitary necrotising granulomas are actually of infectious nature and one must have classical histology in addition to typical clinical findings to support the diagnosis.

Cancer Mimics of Pulmonary Hypertension: Pulmonary Artery Sarcoma

Pulmonary hypertension may be idiopathic or secondary to various causes, including congenital heart failure, pulmonary embolism, or collagen vascular lung diseases [41]. Historically, pulmonary hypertension was thought to result from chronic and sustained pulmonary vasoconstriction, causing shear stress on the walls of the pulmonary arteries and subsequent vascular remodeling. Many forms of human pulmonary hypertension are actually characterised by prominent muscularisation of the pulmonary arteries with partial or complete obliteration of arteries lumen by a conglomerate of cells, referred to as plexiform vascular lesion, that includes endothelial cells, smooth muscle cells, lymphocytes and mast cells [42]. Pulmonary hypertension may be observed in patients with cancer, especially in case of thrombotic or neoplastic embolism.

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). Endovascular biopsy is feasible to obtain the diagnosis.

Pulmonary artery sarcomas mainly develop in patients in their fifth to sixth decade [43, 44]. Symptoms related to vascular obstruction typically mimic pulmonary embolism, with dyspnea, chest pain, cough, and haemoptysis. Failure of anticoagulants in this setting, persistence of pulmonary hypertension, as well as association to weight loss and fever (arising in 40 % of cases), may also suggest the diagnosis.

Imaging findings also help for the differential diagnosis with chronic pulmonary embolism: CT scan also shows a polypoid filling defect in the pulmonary artery, but contrary to thromboembolic disease, sarcoma forms a contiguously soft, smooth, tapering tissue, with possible extravascular nodular spread in the parenchyma (40 % of cases), and localised ground glass opacities (Fig. 35.3) [44]. Sarcoma also presents with a heterogeneous appearance including areas of necrosis and haemorrhage, and with intense hyperactivity on FDG-PET scan [45]. Magnetic resonance imaging shows T1-weighted heterogeneous enhancement, T2-weighted peripheral enhancement, and increased uptake of gadolinium, which are not found in emboli.

Surgery is the only potentially curative treatment and, even if performed in an emergency setting in case of acute right heart failure, allows resectability in 60–75 % of cases [46]. Adjuvant chemotherapy may be administered, espe-

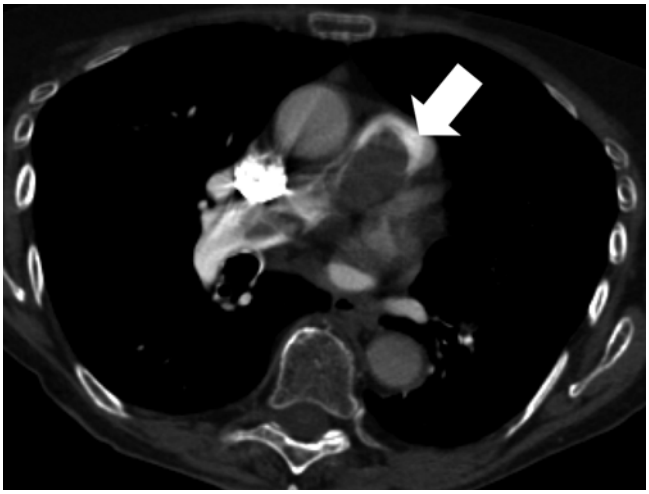

Fig. 35.3 Primary pulmonary artery sarcoma. Computed tomography scan of a 79 years-old woman, which shows complete obstruction and enlargement of the pulmonary artery trunk. Hypermetabolism is detected at 18-fluoro-desoxy-glucose positron emission tomography scan. The patient underwent pulmonary endarteriectomy, complete resection of the tumor, and extensive left pneumonectomy. The patient died 25 months after surgery

cially in incomplete resection, with limited evidence from the literature. Contrary to soft tissue sarcomas, prognosis is mainly related to tumor location, because half of the patients die as a result of the progressive obstruction of the pulmonary trunk [45, 46]. Reoperation is feasible in 30 % of cases. However, in recent series, overall median survival is as low as 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 entity of the pulmonary pseudotumors. The term "inflammatory myofibroblastic tumor" was proposed in 1990 by Pettinato et al. [7, 8, 47], 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" [2, 7, 8, 47]. IMT is rare, with a prevalence of 0.04 % of resected pulmonary neoplasms in the surgical series of the Mayo Clinic [7]. Sub-classifying IMT meets with the fact that both benign and malignant features are observed, representing an archetype of neoplastic/non-neoplastic borderline disorder [3, 6].

Pathologic Features

IMT macroscopically appears either as an intraparenchymatous well-circumscribed mass of variable size [47–49]. Histologically, the tumor is made of irregular proliferation of fibroblasts and myofibroblasts intermixed with an infiltrate of inflammatory cells, mainly lymphocytes and plasma cells. Three major distinct histological patterns are usually recognised [7, 8, 47–49]: (1) the "plasma cell" - also called "lymphoplasmocytary" – variant, composed of inflammatory myxoid proliferation with fascicles of spindled fibroblasts or myofibroblasts, abundant lymphocytes and plasma cells, and minimal fibrous connective tissue; (2) the "fibrohistiocytic" type, showing a compact spindle-cell pattern simulating fibrous histiocytoma, and characterised by a myxoid proliferation of fibroblasts and myofibroblasts associated with polyclonal plasma cells, xanthoma cells, and rare giant cells; and (3) the "organising pneumonia-like" type, with a hypocellular pattern characterised by dense collagen with sparse spindle cells. 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. Differential pathological diagnosis includes all the diseases composed of fibroblasts and myofibroblasts, some of which may overlap with IMT [8]: benign and malignant fibrous histiocytoma, myofibroblastoma, inflammatory fibrosarcoma, spindle cell carcinomas, plasmacytoma, as well as organising pneumonia.

Pathogenesis

The concept of IMT as a proliferating neoplasm has been questioned [8]. Historically, IMT – then called "inflammatory pseudotumor" – was thought to originate from organising pneumonia through exaggerated inflammatory response to injury. Older case reports emphasised that, in as many as 30 % of cases, chronic or repeated infections could be a potential cause, but this concept was reconsidered with more recent reports that included CT-scan studies, suggesting that recurrent pulmonary infections were rather a consequence of bronchial obstruction by the tumor [7, 48].

The concept of IMT as an immunologic disorder was raised after the anecdotic detection of EBV and human Herpes simplex Virus-8 sequences in myofibroblastic cells, with associated expression of cytokines such as interleukin (IL) 6, IL8 and cyclin D1 [7, 50]. The recent identification of immunoglobulin (Ig) G4 expression in polyclonal plasma

cells extracted from intrathoracic IMTs led to consider that an immunopathological process may participate in the development of these tumors, especially the plasma-cell variant ones. Such proliferation of IgG4-positive cells has also been associated with auto-immune disorders including sclerosing pancreatitis, retroperitoneal and mediastinal fibrosis [51]. IMTs may then be part of IgG4-related disease, newly recognized fibroinflammatory condition characterised by tumefactive lesions, a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, storiform fibrosis, and, often but not always, elevated serum IgG4 concentrations.

Molecularly, myofibroblasts are considered as pivotal in the development of IMT. Clonal gene rearrangements may be observed at caryotype [52], especially involving the *Anaplastic Lymphoma Kinase* (*ALK*) gene located in region 2p23 [53]. Diffuse ALK overexpression is observed in 40–70 % of IMTs at immunohistochemistry, but may also be identified -usually at lower levels- in a wide variety of non-IMT soft tissue tumors. *ALK* rearrangement is identified in 40–50 % of IMT cases, especially in younger patients, and most frequently consists of t(1;2)(q21;p23) translocation implicating the *tropomyosine 3* gene [54]. Given the oncogenic nature of *ALK* activation, these data lead some authors to consider IMT as a true neoplasm. Other elements further reinforce this concept, including the presence of vascular invasion, the local recurrence rate as high as 25 % [7], the existence of multifocal lesions in 5 % of cases, reports about malignant transformation, and genomic and expression profiling data, showing DNA aneuploidy, P53 expression, and implication of other known oncogenes such as *glutathione-S-transferase* [55]. Overlap exists between IMT, IgG4-related disorders, and inflammatory fibrosarcoma that exhibits prominent cellular atypias and necrosis.

Clinical-Radiological Features

Clinically, pulmonary IMTs mostly occur before the fourth decade, while accounting for more than 50 % of pulmonary tumors in children [7, 48, 56]. Patients are asymptomatic in about 60 % of cases, or may present with non-specific symptoms including chronic cough, dyspnea or rarely haemoptysis. At imaging, IMT appears as a solitary well-circumscribed peripheral mass, ranging from 2 to 15 cm in size (Fig. 35.4). Contrary to extra-thoracic locations, pulmonary IMT is usually solitary. Calcifications are observed in 15 % of cases.

The usual stability in size over time is an important imaging feature. Multifocal and bilateral IMTs are exceptional, and are considered as overlapping forms of low-grade fibrosarcoma or malignant fibrous histiocytoma. IMTs are usually hypermetabolic at 18-fluorodeoxyglucose-positron emission tomography (FDG-PET)-imaging. Extra-pulmonary involvement occurs in 10–20 % of cases, and is mostly observed in the mediastinum and the pleura. Conversely, extra-pulmonary IMTs may metastase to the lung, especially in younger patients.

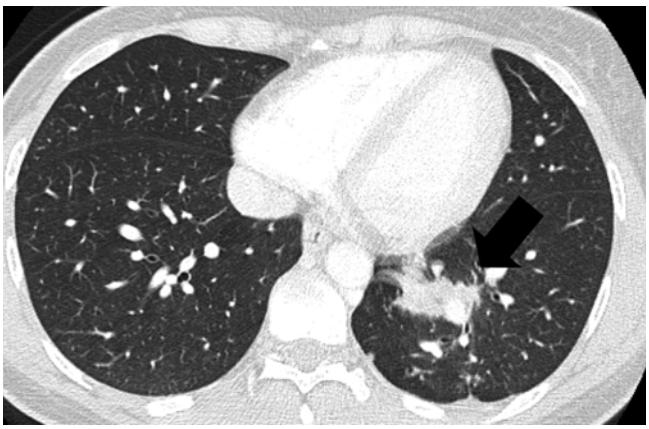

Fig. 35.4 Inflammatory myofibroblastic tumor. Computed tomography scan of a 31 year-old man who presented with persistent cough and haemoptysis following infectious pneumonia. A spiculated mass is located in the left lower lobe. Transparietal biopsy showed polymorphic inflammation without tumor cells. 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

Preoperative diagnosis with endoscopic or per-cutaneous biopsies remains difficult due to the heterogeneous morphology of IMTs. Cytological fine-needle aspiration accuracy was as low as 42 % in a recent study [57].

Treatment

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 haemoptysis and infection, and to potentially relapse with local, pleural, parietal, or mediastinal invasiveness (15–25 % of cases and 3–5 % of cases, respectively) [7, 58, 59]. The need for adjuvant treatment in case of incomplete resection has not been evaluated. In non-operable patients, focal conformation radiotherapy or corticosteroid challenge 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 [59]. In recurrent or multifocal lesions, chemotherapy may use the same regimens as for soft-tissue sarcomas. Crizotinib (PF-02341066, XALKORI™; Pfizer, NYC, NY), a small pharmaceutical tyrosine kinase inhibitor of ALK, was recently reported to produce tumor responses in 2 patients with *ALK*-rearranged extra-thoracic IMTs [60].

Prognosis

Patients with a resected inflammatory myofibroblastic tumor have a 5-year overall survival ranging from 75 to 100 % [7, 57–60]. Transformation to low- and/or high-grade fibrosarcoma has exceptionally been reported, and may correspond to initially misdiagnosed high-grade tumors [2, 58]. ALK-positive tumors are considered to be more aggressive, but

local recurrence actually occurs regardless of ALK expression level [53]. The most consistent prognostic factor is actually the initial invasiveness of the tumor.

Overall, IMT, while having been considered for a long time a reactive lesion simulating a neoplasm, is now rather regarded as a true low-grade neoplasm. However, other pseudotumors are described in adults, of diverse pathogenesis [4, 6]. Moreover, several entities related to IMT have been described, including sclerosing mediastinitis and hyalinising granuloma.

Sclerosing Mediastinitis and Hyalinising Granuloma

Similar to IMT, sclerosing mediastinitis and hyalinising granuloma both consist of tissular infiltration by dense collagen fibrosis forming lamellar bands, interspersed with lymphocytes and plasma cells [61–63]. 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. Overlap exists between these entities and other fibrosing disorders such as IMT, retroperitoneal fibrosis, and other IgG4-related disorders.

Sclerosing Mediastinitis

A hallmark of sclerosing mediastinitis is the obstruction of major mediastinal veins, with multifocal venous infarcts observed in the tumor leading to lumen obstruction by cellular fibrosis, haemorrhage, and necrosis. Sclerosing mediastinitis has mostly been described in North America, where it is thought to result in most cases from exacerbated response to *Histoplasma* [64]. Sclerosing mediastinitis may actually be idiopathic, familial, or associated with various disorders, including other fungal infections – aspergillosis, cryptococcal infection -, tuberculosis, or sarcoidosis. It has also been described following radiation therapy, ergot derivatives, or beta-blockers treatment. Autoimmune reaction may also participate to the development of sclerosing mediastinitis, as association with elevated serum IgG4 syndrome has been reported [65].

Clinically, sclerosing mediastinitis is observed in the fourth decade, with a slight male predominance. Patients may be asymptomatic or develop chest pain, fever, haemoptysis, dyspnea, as well as signs related to mediastinal structures invasion; venous infarcts of the lung can be the first manifestation of the disease. The amplitude of symptoms is actually related to the extension of the sclerosis. At imaging, sclerosing mediastinitis presents either as a localised and calcified mass in the paratracheal, hilar, or subcarinal areas, or as a diffuse infiltrate of the whole mediastinum, with no calcification (Fig. 35.5). The lung may be marginally affected, with consolidation areas associated with venous infarcts, and possible pleural effusion.

Treatment of sclerosing mediastinitis consists of surgical resection, which may often be only palliative given the extent of the fibrosis. Surgical biopsy is actually often necessary to obtain a definite diagnosis. Prognosis depends on the structures involved. Steroids and cyclophosphamide are of little efficacy in extensive forms.

Hyalinising Granuloma

Hyalinising granuloma is rare and occurs in young to middle-aged adults with a slight predominance in men [66]. Patients usually have symptoms (80 % of reported cases), consisting of cough, dyspnea, and pleuritic chest pain. Association with

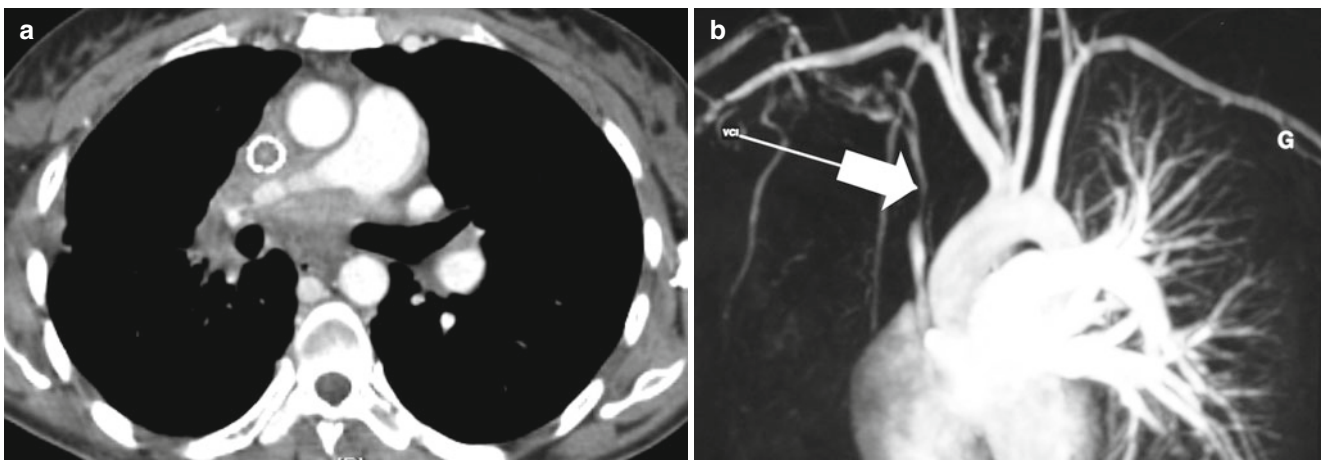

Fig. 35.5 Sclerosing mediastinitis. (**a**) Computed tomography scan of a 32 year-old woman who presented with progressive dyspnea and superior vena cava syndrome. Connective tissue proliferation infiltrates the entire mediastinum. Surgical biopsy was performed to make the diagnosis. (**b**) At magnetic resonance angiography, the calibre of the superior vena cava is reduced (*arrow*). An endoprothetic tube was placed as palliation

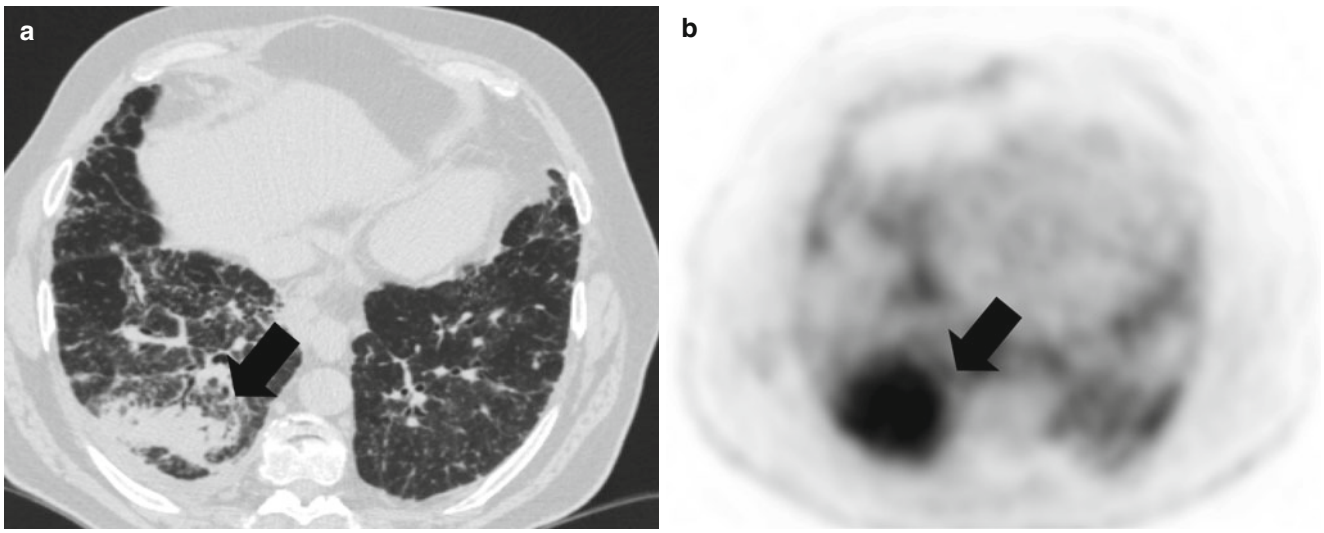

Fig. 35.6 Hyalinising granuloma. (**a**) Computed tomography scan of a 62 year-old man with a history of sarcoidosis, chronic obstructive pulmonary disease, emphysema and liver transplantation for cirrhosis, who presented with right lower lobe parenchymal condensation (*arrow*). (**b**) 18-fluoro-desoxy-glucose positron emission tomography showed increased uptake of the mass (*arrow*). The patient presented with recurrent spontaneous pneumothorax and underwent thoracoscopy for pleurodesis. Resection of the lesion was done, leading to the diagnosis of hyalinising granuloma

other sclerosing diseases has been reported, including sclerosing mediastinitis (15 % of cases) and retroperitoneal fibrosis (10 % of cases). The radiologic presentation is that of solitary or multiple well-circumscribed lung nodules, usually 2–4 cm in size, which may grow over time and thus mimic cancer. The lesion may be found in the context of sarcoidosis and IgG4-related disease (Fig. 35.6) [67]. The main differential diagnosis is nodular amyloidosis, as factitious Congo red positivity may occur. The clinical course is benign.

Other Pseudotumors

The most common mechanism causing the development of a pseudotumor is thought to be reparative or post-traumatic through exaggerated host response to injury. Developmental pseudotumors include benign lesions such as hamartomas, leiomyomas, and choristomas [4, 6]. Tissue remnants or heterotopias related to embryologic variation is another etiologic group, the most frequent entity being minute meningioma-like nodules that correspond to glial heterotopias [68]. Similarly, clear cell tumors – also called "sugar tumor" – are derived from perivascular epithelioid cells of the lung epithelium; these cells are of neuroectodermal origin, and are also implicated in the development of perivascular epithelioid cell (PEC) tumor and lymphangioleiomyomatosis.

Functional pseudotumors are related to dysfunctional patho-physiological state, often of endocrine nature, and are rare in the lung parenchyma. Iatrogenic pseudotumors are due to several medical procedures that can produce tissue reactions, most of which are reparative in nature. Infectious pseudotumors may be produced by mycobacteriae (tuberculoma), fungal agents (aspergilloma), or even viruses (EBV, HIV, Cytomegalovirus). The pathogenesis of these tumors may be complex, possibly implicating multiple mechanisms. The clinical and radiological features of these tumors may be similar to that of IMT.

Borderline Neoplastic-Non Neoplastic Disorders

Borderline Benign Tumors

Excluded from this chapter are benign tumors and preneoplastic conditions of the lung, which have extensively been reviewed elsewhere [5]. Borderline neoplastic and non-neoplastic disorders include entities that are considered benign despite being associated with true neoplasm 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.

Mesenchymal Borderline Disorders

Some benign lesions, presenting a slow-growing intraparenchymal masses with homogeneous attenuation and regular contours, may present with clonal chromosomal aberrations. For example, hamartomas may exhibit gene rearrangements in regions 12q15 and 6p21 [69]. These

regions contain the *high mobility group AT-hook* genes, respectively, encoding non-histone nuclear proteins that participate to the regulation of gene expression via alteration of chromatin structure. Interestingly, similar alterations have been described in other mesenchymal tumors. Similarly, multiple minute pulmonary meningothelial-like nodules, which are millimetric nodular proliferations of oval to spindle-shaped cells resembling meningioma and arranged in a nested pattern, exhibit loss of heterozygosity (LOH) in multiple genomic loci in 33 % of cases [70]. Relationship of minute meningothelial-like nodules with primary pulmonary meningioma is not certain, given the contrast between the relatively high prevalence of meningothelial-like nodules and the low frequency of meningioma as a primary lung tumor.

Papillomatosis

Ultimately, some benign lesions may have a borderline presentation and outcome. One relevant example is recurrent respiratory papillomatosis. Papillomas usually occur in the upper respiratory tract, but may rarely spread to the lung parenchyma (less than 5 % of cases) [71, 72]. 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. Squamous papillomas are lined by stratified squamous epithelium, sometimes keratinised. Distal papillomas exhibit a more inverted growth pattern. Overall, papillomas may exhibit similar imaging features as lung cancer, including heterogeneous, cavitating, or poorly defined masses.

Pulmonary papillomas may be solitary or multiple; then 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 [73]. Specifically, HPV type 11 infection has been reported as bearing a high-risk of transformation of papilloma to squamous cell carcinoma [74]. Molecularly, loss of the tumor suppressor genes *TP53*, *RB* and *P21* has been reported in squamous cell carcinomas originating from papillomas. Duplication of promoter and oncogene regions in the virus may occur [75]. Pathologically, distinction with invasive squamous cell carcinoma can be difficult in some exophytic cases or atypical cytology. Given this uncertain malignant potential, and the difficult differential diagnosis with lung cancer, complete resection of papillomas is then recommended, but may not be possible in case of multiple and bilateral lesions. 18-FDG-PET scan may not be useful in this setting, given the mild hypermetabolism of high grade papillomas. Vorinostat, a histone deacetylase inhibitor, was reported to produce tumor control in the setting of HPV11-related lung cancer [75].

Nodular Lymphoid Hyperplasia

Pulmonary nodular lymphoid hyperplasia (NLH) – historically called "pseudolymphoma" is a nodular reactive polyclonal lymphoid proliferation infiltrating the lung, characterised by low-grade histology, presence of lymphoid follicles, and a benign clinical course [76]. Recent advances in immunophenotypic and molecular characterisation of lymphoproliferative disorders led to consider most of reported observations of NLH as misdiagnosed nodular marginal zone B-cell lymphomas. However, there remain a number of lymphoid proliferations in the lung for which clonality is not demonstrated even after molecular gene rearrangement studies, flow cytometry, and immunoglobulin expression at immunohistochemistry [76]. Histologically, NLH corresponds to lymphoid follicles with intercalated prominent plasma cells and usually mild interstitial fibrosis. Lymphangitic distribution of lymphocytes and plasma cells may occur around the bronchovascular bundles and interlobular septa. Immunohistochemistry shows a mixture of polytypic B and T cells. No immunoglobulin heavy chain gene rearrangement is identified. Differential diagnoses are MALT lymphoma, lymphocytic interstitial pneumonia, lymphomatoid granulomatosis; overlap entities, such as "atypical lymphoid proliferation" have also been described. Peribronchial lymphocytic infiltrates are also observed in Sjögren syndrome, that may be associated with true lymphoma.

In a series of 14 well-characterised NLH published in 2000 [76], most patients (81 %) were asymptomatic. Radiologic presentation was that of a solitary peripheral nodule in 9 patients – median size was 3 cm -, and was multifocal in 5 patients. Five patients (36 %) also had concomitant hilar, mediastinal, or paraesophageal lymphadenopathy. Treatment consisted in surgical resection, in most cases in the initial hypothesis of lung cancer. Interestingly, no recurrence or progression to more aggressive lymphoproliferative disease was documented, stressing the specific nature of NLH.

Amyloid and Non-amyloid Immunoglobulin Deposition Disorders

Amyloidosis is characterised 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 polarised light [77]. Amyloidosis has a highly variable clinical-radiological presentation. The lung parenchyma is involved in 30–80 % of cases. Pulmonary amyloidosis may be localised 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 [77–79]. Patients are usually asymptomatic. The lesion is solitary in about 30 % of cases, corresponding to so-called amyloidoma. When multiple nodules are present, symptoms may include cough, haemoptysis, or pleuritic chest pain due to pleural effusion. Radiologically, pulmonary nodules are rounded and sharply delimited usually mimicking neoplastic growth [78]. 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 [77–79]. 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 [77]. 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 [77]. 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, most patients present with concomitant cardiac amyloidosis, 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.

Likewise amyloidosis, nonamyloidotic monoclonal immunoglobulin deposition disease (NAMIDD) initially described in the kidney where it is referred to as Randall's disease, was recently reported to occur in the lung [80–82]. NAMIDD presents with deposits that are not stained by Congo red dye and do not demonstrate birefringence under polarised 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 impairement, which may be severe [80, 81]. Approximately half of the cases are associated with hematologic malignancies, mostly of lymphoplasmacytic nature [80]. Pulmonary NAMIDD may benefit from lung transplantation in cases of severe respiratory failure and in the absence of an underlying hematologic disorder [81].

Pulmonary Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is a heterogeneous disease defined by the proliferation of Langerhans cells, corresponding to CD1a-positive histiocytes exhibiting Birbeck granules at electron microscopy [83, 84]. These cells of dendritic lineage derive from CD34-positive bone marrow stem cells. The lung may be the sole location of the disease – then called "pulmonary LCH". In less than 15 % of cases, pulmonary LCH is associated with multisystem disease, corresponding to "acute disseminated LCH" involving the bone, the skin, and the pituitary gland [85].

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, and is thought to stimulate this process in the bronchiolar epithelium [86]. The true nature of LCH remains elusive. Strongly favouring the hypothesis of a neoplastic disorder is the observation that Langerhans cells, isolated either from pulmonary or disseminated LCH patients, are clonal [87]. Activating *BRAF* mutation –similar to that observed in melanoma- may be identified in LCH pulmonary nodules [88]. 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 strongly taper the 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 characterised by disappearance of Langerhans cells, increased amounts of fibrosis, and cavitation of the nodules leading to cyst formation [83].

Clinically, pulmonary LCH occurs in young smokers who present with non-specific respiratory symptoms, including

dyspnea, cough, and chest pain. Pneumothorax may reveal 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 [83–85]. Nodules, ranging from 5 mm to 2 cm in size, are centrilobular, may be solid or cavitated, with smooth or irregular margins. LCH is an active process, with predominant nodular aspect at early stages of the disease, evolving to cavitated nodules, thin-walled cysts, and confluent cystic lesions over time. Lesions of different age are usually observed. Rarely, pulmonary LCH presents as a single nodule, localised consolidation, or mediastinal disease.

Whereas pulmonary LCH may be virtually diagnosed facing a typical clinical-radiological presentation, pulmonary biopsy may be required in case of tumor-like nodular presentation. Open lung biopsy is usually performed in patients with pneumothorax that require surgical intervention. FDG-PET results in LCH may spuriously suggest lung cancer; in a recent study of 11 patients, nodular lesions exhibited hypermetabolism, with maximum standardised uptake value ranging from 2 to 18 [89]. FDG-PET might reveal useful in the follow-up of the activity of the disease and is the subject of current research. No treatment has been prospectively confirmed to be useful in pulmonary LCH, which may regress spontaneously or after smoking cessation in as many as 25 % of patients. Patients with progressive or multiorgan disease may benefit from chemotherapy with cladribine (Leustatin, Ortho Biotech, Raritan, NJ), that produced a 75 % objective response rate in a landmark study of 13 patients [90, 91]. Supporting the neoplastic hypothesis, pulmonary LCH can recur following lung transplantation despite aggressive immunosuppressive therapy.

Lessons Learned

The management strategy for rare intrathoracic tumors is close to that of rare pulmonary diseases [3]. As discussed above, some clinical and radiological features, although infrequent, may strongly suggest or challenge the diagnosis, such as air bronchogram in MALT lymphoma, organising pneumonia, and bronchioloalveolar carcinoma, or recurrent "pulmonary embolism" despite well-conducted treatment in pulmonary artery sarcoma.

The main differential diagnosis of rare pulmonary tumors is lung cancer. The absence of 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 feature to consider, because more than 50 % of pseudotumors occur before the fourth decade. Given the frequent initial suspicion of lung cancer, most patients undergo complete oncological workup. As shown above, 18-FDG-PET scan may frequently be positive in pseudotumors, leading to further support the hypothesis of lung carcinoma. Preoperative biopsies and intraoperative frozen sections may not be sufficiently representative of the tumor to ensure accurate histopathological diagnosis, especially in biphasic or composite tumors, for which small-size samples may identify only one cellular component. Sophisticated pathological studies, including flow cytometry, molecular and cytogenetic analysis, may have a critical role both in diagnosis, evaluation of tumor grade, and therapeutics, such as for lymphoma, IMT, or sarcomas. Frozen specimen collection and storage is mandatory for additional analyses.

In many cases, upfront surgical resection provides the correct diagnosis and the first-step of the therapy. However, preoperative diagnosis remains important for specific subtypes, such as lymphoma, for which extensive resection is not systematic, and for sarcoma, which usually does not spread to the mediastinal lymph nodes and thus does not require nodal resection. Surgical biopsy may be required to obtain sufficient amount of tissue material for extensive pathological and molecular diagnoses, especially when clinical-radiological presentation is not typical of neoplastic or non-neoplastic disease.

Finally, three main clinical scenarios may arise in the diagnostic setting of patients with rare lung tumors or pseudotumors: (1) Surgical resection of the tumor has been complete, and pathological examination disclosed an unusual or borderline histopathological subtype; then no adjuvant therapy or follow-up is recommended in the absence of systemic metastasis; (2) Specific clinical and radiological signs led to recognition of a rare tumor, such as lymphoma or pulmonary artery sarcoma, followed by specific diagnostic and therapeutic management; (3) Surgery of a pulmonary mass initially thought to be lung cancer led to the identification of a rare tumor subtype, and therapeutic and prognostic implications are unknown. Further characterisation, including molecular analyses, are then mandatory to evaluate the degree of malignancy, including clonality analyses – such as in lymphoproliferative disorders -, and mutation analyses – such as in IMT -, that may have diagnostic and predictive value for therapeutics. In the absence of evidence-based recommendations, multidisciplinary consensus management at expert centers is mandatory for the selection of a specific therapeutic strategy, possibly based on strategies developed for lesion of similar histology arising in other anatomic location. Molecularly tailored treatment may be useful. Also, these issues emphase the need for multicenter collaboration to generate cohorts and to launch observational studies in the field.

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Rare Diffuse Lung Diseases of Genetic Origin

36

Paolo Spagnolo

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

Clinical Vignette

A 48-year-old Italian lady was seen in our outpatient clinic in April 2010. She reported a 2 year history of progressive dyspnea and decreased 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; she was clubbed and had widespread velcro-type end-inspiratory crackles on 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 affecting particularly the upper zones (Fig. 36.1). Lung function tests showed a restrictive 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 until she died 11 months later while listed for lung transplantation.

Pulmonary fibrosis may occur in the context of several genetic disorders displaying a wide spectrum of apparently unrelated clinical manifestations, the most common ones being dyskeratosis congenita and Hermansky-Pudlak syndrome. Dyskeratosis congenita is typically associated with skin hyperpigmentation, oral leukoplakia, and nail dystrophy, none of which were present in this patient. Instead, a history of bruising, heavy menstrual cycles and fair skin in a patient with lung fibrosis is strongly suggestive of Hermansky-Pudlak syndrome. In this patient the diagnosis was confirmed by sequencing analysis, which revealed a mutation within HPS1 gene.

Disorders caused by the inheritance of a single defective gene are known as *monogenic* or single gene disorders. Monogenic diseases, which may be either "recessive" (i.e., they produce symptoms only if a defective copy of the gene is passed on by both parents) or "dominant" (i.e., they only require one defective copy of the gene to be inherited in order to occur), are generally due to specific and relatively rare *mutations* often leading to a single amino acid change in an encoded

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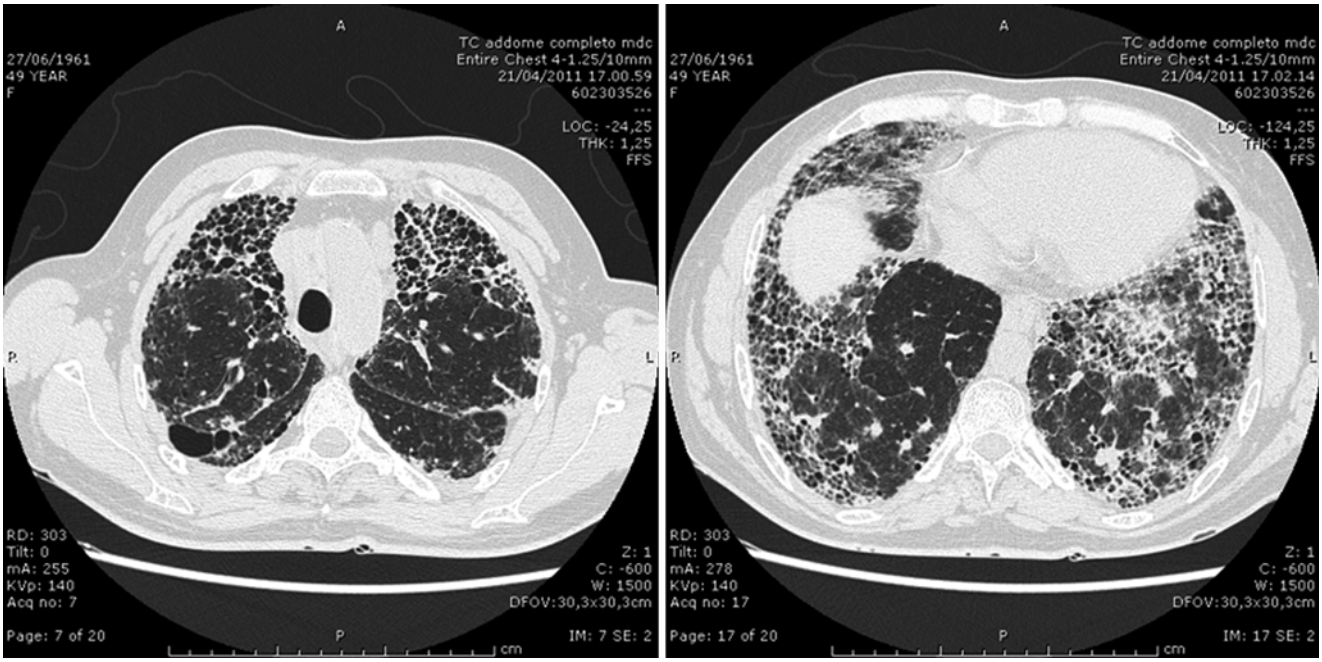

Fig. 36.1 Hermansky-Pudlak syndrome. CT images through upper and lower lung zones showing extensive subpleural honeycombing bilaterally, more prominent in the lower lung zones where ground glass opacity is also present

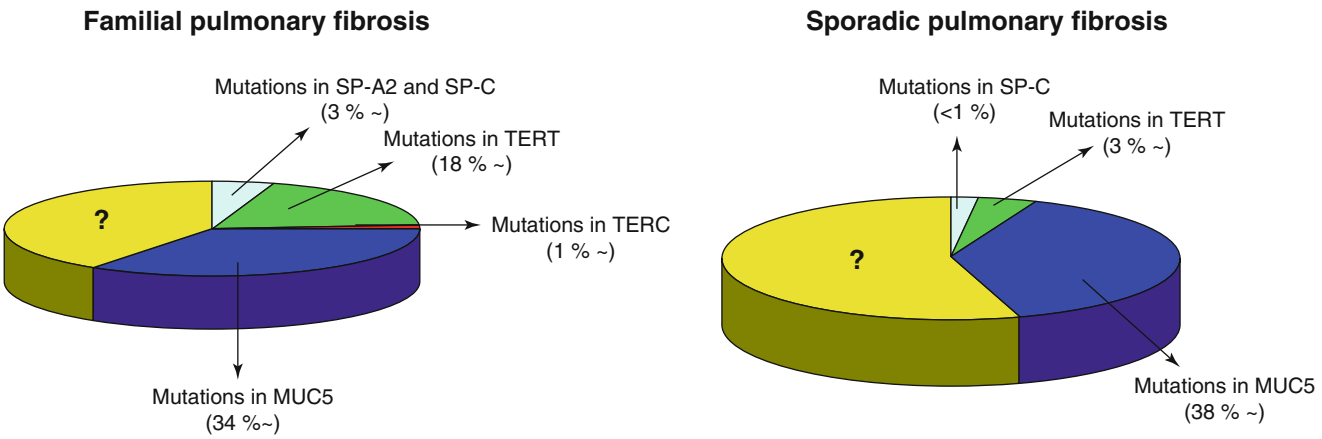

Fig. 36.2 Estimated frequencies of genetic mutations in familial and sporadic cases of pulmonary fibrosis

protein. Conversely, *complex* diseases result principally 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, complex diseases are thought to have significant genetic as well as environmental components.

Unlike cystic fibrosis, which is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, the genetic of diffuse parenchymal lung disease is complex. For example, idiopathic interstitial pneumonia display considerable genetic heterogeneity and both rare mutations (within surfactant protein C, surfactant protein A2, telomerase reverse transcriptase and telomerase RNA component genes [1–7]) and common variants (MUC5B gene [8]) have been associated with the risk of developing the disease (Fig. 36.2). In familial forms of pulmonary fibrosis many of the pedigrees show vertical transmission consistent with a genetic pattern of autosomal dominant inheritance with reduced penetrance. Interestingly, 45 % of the pedigrees display phenotypic heterogeneity, suggesting that the underlying genetic factors cause an increased *generic* predisposition for pulmonary fibrosis, and not a predisposition for a specific disease subtype [9].

Hermansky-Pudlak Syndrome

Hermansky-Pudlak syndrome (HPS) is a rare autosomal recessive disorder most commonly found in persons from Puerto Rico characterized by oculo-cutaneous albinism,

bleeding diathesis, and accumulation of ceroid, a chromolipid related to lipofuscin, in the reticuloendothelial system of various tissues [10, 11]. Seemingly disparate, these abnormalities are presumably related to defective formation, trafficking, or function of intracellular lysosome-related organelles: melanosomes (oculocutaneous albinism), platelet dense bodies (bleeding dysfunction), and lysosomes (ceroid lipofuscin deposition; [12]). The disease can also be complicated by lung fibrosis, neutropenia and granulomatous colitis.

HPS comprises nine known disorders (HPS-1 to HPS-9), the majority of which present with the same clinical phenotype to varying degrees of severity. Prevalence is estimated at in 1,800 in northwestern Puerto Rico – making it the most common single-gene disorder amongst this population – with only isolated case reports and small case series being reported in the rest of the world [13]. HPS can be caused by mutations in one of several genes: HPS1 (10q23.1), 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). The majority of Puerto Rican patients demonstrate a homozygous 16 base pair duplication in the HPS1 gene, reflecting a founder effect. This genotype represents the most severe of the known mutations and accounts for a high risk of pulmonary disease, hemorrhage, and granulomatous colitis [14]. Once the diagnosis has been confirmed – by means of genotyping, demonstration of absent dense bodies on whole mount electron microscopy of platelets, or accumulation of ceroid in pathological specimens – other family members should be screened for the syndrome and mutations within genes known to cause the disease searched for [15, 16].

Pulmonary fibrosis, the most serious complication, usually presents in the third or fourth decade, appears to be more common in women and affects up to 80 % of all cases with HPS subtypes 1 and 4 [17]. Dysfunction of lamellar bodies in type II pneumocytes, which synthesize, store, and release surfactant, is probably a contributing factor by causing deposition of ceroid and degeneration and death of type II cells [18]. In addition, the early development of pulmonary fibrosis in HPS suggests that environmental or external insults, acting either alone or coupled with abnormal repair mechanisms, play a major role in producing this complication. Chest radiograph and high resolution computed tomography (HRCT) show nonspecific patterns of diffuse, peripheral reticulation, subpleural cysts, and ground glass opacities. As the disease progresses, peribronchovascular thickening and bronchiectasis develop [19]. Honeycombing, when presents, prevail in the lower lobes but is not predominantly subpleural as in usual interstitial pneumonia (UIP). Similarly, the active fibroblastic foci seen in UIP are generally not present in HPS [20]. HRCT findings tend to differ somehow as the disease progresses. In cases of minimal severity, the most common abnormalities include interlobular septal thickening, reticular opacities, and ground glass attenuation, while in severe cases, subpleural honeycombing and bronchiectasis become the predominant features [19]. Histologic examination, in addition to the extensive fibrosis of the alveolar walls, reveals macrophages filled with ceroid throughout the interstitium and alveolar spaces. Lung disease is the most frequent cause of death, followed by inflammatory bowel disease and bleeding complications. There is no effective treatment for HPS-related pulmonary fibrosis. Although one trial reported delayed disease progression with the anti-fibrotic agent pirfenidone in HPS type 1 patients with forced vital capacity >50 % [21], lung transplantation remains the only potentially life-extending therapy for progressive lung disease.

Telomerase-Associated Pulmonary Fibrosis

Telomeres – the tandem repeats of TTAGGG – represent a molecular cap of non coding DNA that protects the ends of the chromosomes against degradation. With repeated cell division telomeres tend to shorten and the chromosomes may become unstable, fused, or lost, leading to cell apoptosis. A complex of proteins and RNA called *telomerase* is essential in extending telomeres, thus preventing their shortening: the reverse transcriptase component *TERT* and the RNA template component *TERC* are key components of the *telomerase complex* [22]. In addition to age and telomerase function, environmental factors, such as smoking, affect telomere function by reducing their length [23].

Dyskeratosis Congenita

Dyskeratosis congenita (DC) is a rare systemic disease (overall incidence 1 in 1,000,000 persons) usually presenting in the first or second decade with bone marrow failure, the leading cause of death, and a triad of muco-cutaneous lesions including patchy skin hyperpigmentation of the upper chest and neck, dystrophic nails, and oral leukoplakia [24]. DC is considered a syndrome of premature aging as suggested by other common features, such as premature graying of the hair, pulmonary fibrosis, testicular atrophy, cryptogenic cirrhosis, osteoporosis, and increased risk of malignancy. Further corroborating this hypothesis, DC has been the first disease recognized to result from impaired telomere maintenance [25]. Mode of inheritance may be autosomal dominant, recessive, or X-linked, with this latter form resulting from a mutation in the *DKC1* gene, which encodes dyskerin, a telomerase-associated protein. Similarly, there is wide variation in severity and spectrum of manifestations, which is only partially explained by locus and allelic heterogeneity. Affected cases with mutations in the genes for *TERT* and *TERC* often demonstrate genetic *anticipation*, the occurrence of more severe and earlier onset disease in later gen-

erations secondary to the progressive shortening of telomeres [26]. While telomere length is uniformly reduced, thus indicating a shared mechanism, a genetic defect has not yet identified in most patients with DC, an indication of the complexity of the pathways involved in this disease.

Pulmonary fibrosis develops in approximately 20 % of cases. The histology most often demonstrates UIP, although other patterns including bronchiolocentric inflammation and nonspecific interstitial fibrosis have been described. Pulmonary complications often arise after stem cell transplantation used to treat bone marrow failure [25]. Prognosis of DC patients after the development pulmonary fibrosis is poor, with death occurring 12–40 months after the onset of dyspnea [27].

Short telomere length occurs also in familial and sporadic cases of pulmonary fibrosis without other features of DC. In a cohort of subjects with familial interstitial pneumonia 6 of 73 probands (8 %) had heterozygous mutations in *TERT* or *TERC* in circulating lymphocytes [5]. Asymptomatic subjects with mutant telomerase also had short telomeres, suggesting that they may be at risk for the disease. In a larger cohort with both familial and sporadic pulmonary fibrosis, the lymphocyte telomere length was uniformly less than 10 % of age-matched controls in cases with identifiable telomerase-associated mutations. Similarly short telomeres have been found in patients without identifiable mutations. The overall incidence of short telomeres was 25 % of sporadic and 37 % of familial cases of pulmonary fibrosis [4]. Reduced telomere length has also been reported in both alveolar epithelial cells and lymphocytes in sporadic cases of idiopathic interstitial pneumonia – with patients displaying significantly shorter telomeres compared to age-matched controls – even when no telomerase mutations are identified [28]. Furthermore, there is evidence that short telomere length may be a risk factor for disease outside the lung, such as liver cirrhosis or diabetes [28].

Lysosomal Lipid Storage Disease

Lysosomal lipid storage diseases, also known as *lip doses*, are inherited metabolic disorders in which lipids accumulate in cells and tissues. They represent about 70 genetically distinct conditions with a combined birth frequency of about 1 in 7,500 [29]. Complex lipids, such as glycosphingolipids, which have a major structural function in many cell types, are constitutively degraded within the endolysosomal system by soluble hydrolytic enzymes with the help of lipid binding proteins in a sequential manner. Due to a functionally impaired hydrolase or auxiliary protein, their lipid substrates cannot be degraded, accumulate in the lysosome and slowly spread to other intracellular membranes. In most lysosomal lipid storage diseases the accumulation of one or few lipids leads to the co-precipitation of other hydrophobic substances in the endolysosomal system, such as lipids and proteins, causing a "traffic jam", thus impairing lysosomal function, such as delivery of nutrients through the endolysosomal system and leading to a state of cellular starvation.

Gaucher's Disease

Gaucher's disease – the most common lysosomal lipid storage diseases – is an autosomal recessive disorder caused by deficient lysosomal β-glucosylceramidase activity with subsequent tissue deposition of glucosylceramide [30]. Gaucher's disease has been identified throughout the world and among all ethnic groups. The pathologic hallmark is the presence of the so-called *Gaucher cells* in the macrophage-monocyte system, particularly in the liver, spleen and bone marrow. These cells, which are 20–100 μm in diameter, have a characteristic wrinkled-paper appearance resulting from intracytoplasmic substrate deposition, and stain positively with PAS. Gaucher's disease is classified into three broad phenotypes based upon the presence or absence of neurological involvement: Type 1 (*non-neuronopathic*), Type 2 (*acute neuronopathic*), and Type 3 (*subacute neuronopathic*) [30].

The β-glucosylceramidase gene is located to 1q21 and comprises 11 exons and 10 introns, spanning 7.6-kb of sequence. Nearly 300 mutations within the β-glucosylceramidase gene have been identified in Gaucher patients – including frame-shift mutations, point mutations, deletions, insertions, splice site mutations, and recombinant alleles [31] – with a distribution that spans the gene. 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 disease when inherited with a null or another severe mutation. On the other hand, mild mutations, such as c.1226A>G (N370S), are only associated with Type 1 disease [32]. Gaucher patients display a wide spectrum of clinical phenotypes, ranging from asymptomatic adults to children who succumb from devastating neurological disease. Hepatosplenomegaly, haematological abnormalities and orthopaedic complications represent the predominant manifestations [33]. Conversely, pulmonary involvement clinically manifests in less than 5 % of patients with Type 1 disease [34]. Four pattern of pulmonary involvement have been described: intracapillary, patchy interstitial infiltrates in a lymphatic distribution, massive interstitial thickening of alveolar septa, and intra-alveolar infiltrates. Respiratory manifestations, which include recurrent infections leading to progressive dyspnea (often culminating in fatal respiratory failure), 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 or a diffuse reticulonodular infiltrate [35]. L444P homozygotes appear at major risk for developing pulmonary disease, even at an early age [35]. On the other hand, pulmonary hypertension, strongly associated with splenectomy and female gender, may occur in subjects with non-N370S mutation within β-glucosylceramidase gene, positive family history, and angiotensin converting enzyme I gene polymorphism [36]. Despite significant advances in our knowledge of the spectrum of mutations within β-glucosylceramidase gene, our ability to make prognostic predictions from genotypic data remains limited. While it is possible to enumerate individual mutant alleles encountered in patients with Gaucher's disease Type 1, 2, and 3, it is the combination of mutations on both alleles that is important in defining the phenotype. In addition, similar phenotypes may result from different genotypes, while individuals sharing the same genotype can present with and exhibit different disease manifestations, clinical courses and responses to therapy [31]. Gaucher disease is the first lysosomal lipid storage diseases to be successfully treated by enzyme replacement therapy [37]. At present, alglucerase (Ceredase®, Genzyme Inc.), imiglucerase (Cerezyme®, Genzyme Inc.), and velaglucerase alfa (VPRIV™, Shire) have been FDA-approved for treatment of Gaucher patients. However, enzyme replacement therapy, which consists of intravenous infusions of recombinantly produced glucocerebrosidase, is a costly and lifelong treatment. In addition, in contrast to the remarkable effect on hepatosplenomegaly and haematological abnormalities, pulmonary manifestations (clinically, functionally, and radiologically) appear to respond only poorly to enzyme replacement therapy [38]. Similarly, because it does not cross the blood-brain barrier, enzyme replacement therapy does not prevent or halt neurologic involvement.

Niemann-Pick Type Disease

The eponym "Niemann-Pick disease" (NPD) is commonly used to designate a heterogeneous group of autosomal recessive lysosomal lipid storage diseases that share the general clinical and biochemical features of hepatosplenomegaly, with varying degrees of sphingomyelin and cholesterol accumulation in reticuloendothelial and parenchymal tissues, with or without neurological involvement [39]. NPD is commonly classified in three major subgroups: type A is characterized by severe, early central nervous system deterioration and massive visceral and cerebral sphingomyelin storage resulting in death in the first few 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 a milder visceral storage. NPD types A and B are caused by mutations in the sphingomyelin phosphodiesterase 1 gene (11p15.1–11p15.4) that result in deficient lysosomal acid sphingomyelinase activity. Of the mutations in the sphingomyelin phosphodiesterase 1 gene causing types A and B NPD only a few occur frequently. Instead, most of them are "private," having been described only in one or a few families. Frameshift mutations, small and large insertions and deletions and splicing defects typically have 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 [40]. Inheritance of two type A alleles predicts a type A phenotype with a neurodegenerative disease course. In contrast, inheritance of one type B allele is neuroprotective and predictive for a type B phenotype, even if the other allele has a type A abnormality. Niemann-Pick C (NPC) disease is a neurovisceral lysosomal lipid storage diseases characterized by abnormal intracellular transport of endocytosed cholesterol with sequestration of unesterified cholesterol in lysosomes and late endosomes [41]. The disease is transmitted in an autosomal recessive manner and is caused by mutations in either *NPC1* (18q11-q12, 95 % of cases) or *NPC2* (14q24.3) genes, with nonsense or frameshift mutations within *NPC1* being associated with the most severe neurological course. Although the precise functions of the NPC1 and NPC2 proteins are still elusive, they are thought to function in a coordinate fashion in the cellular post-lysosomal/late endosomal transport of cholesterol and other molecules [42, 43]. The clinical presentation of NPC disease is extremely heterogeneous, with an age of onset ranging from the perinatal period until well into adult age. Likewise, the lifespan of the patients varies between a few days until over 60 years of age, although the majority of cases die between 10 and 25 years of age. Apart from a small subset of patients who die at birth or in the first 6 months of life from hepatic or respiratory failure, all patients will ultimately develop a progressive and fatal neurological disease, which manifests mainly with cerebellar ataxia, dysarthria, dysphagia, and progressive dementia. The majority of cases show also a characteristic vertical supranuclear gaze palsy. Systemic disease – in the form of liver, spleen and lung involvement – always precedes the onset of neurological symptoms [44].

Pulmonary disease most often presents with features of endogenous lipoid pneumonia – with the typical foamy-appearing macrophages containing sphingomyelin (Figs. 36.3 and 36.4) – or, interstitial fibrosis, which produce either a miliary or a reticulo-nodular appearance on the chest radiograph [45, 46]. Niemann-Pick cells (sea-blue histiocytes) are seen in bronchoalveolar lavage fluid [47]. One series of 53 patients with type B disease found evidence of interstitial abnormalities on HRCT in 98 % of cases: upper lobe predominant ground glass opacities and basilar predominant interlobular septal thickening were the most common features (Figs. 36.5 and 36.6) [45]. Pulmonary function

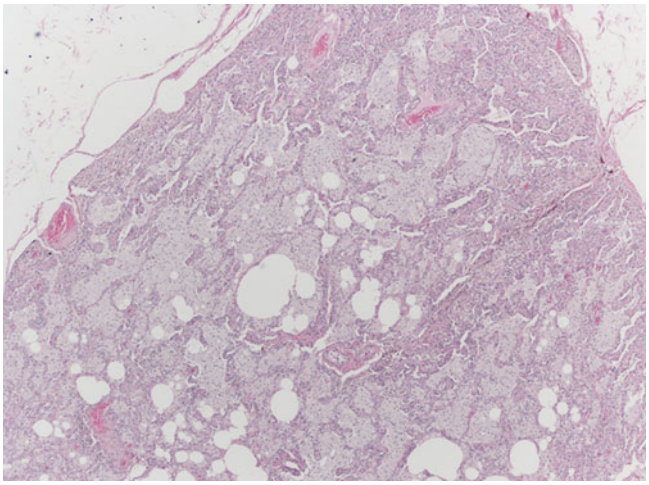

Fig. 36.3 Surgical lung biopsy in a 33-year-old woman with type-B Niemann-Pick disease. At low magnification, alveoli are filled with pale-staining macrophages (hematoxylin-eosin, 20×) (Slide courtesy Alberto Cavazza, MD)

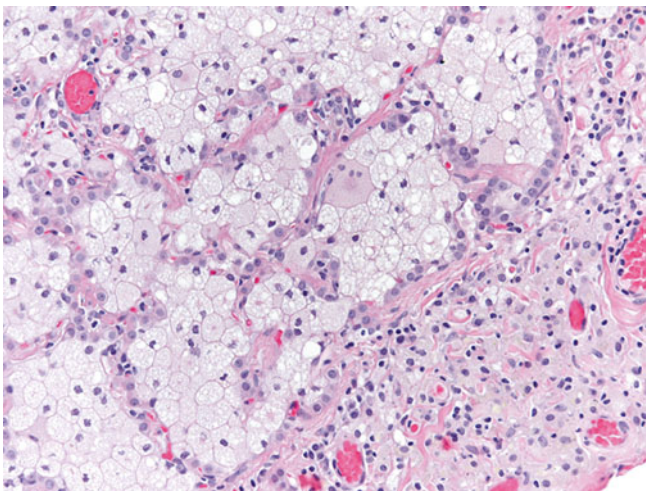

Fig. 36.4 Higher magnification showing the finely vacuolated cytoplasm of the intra-alveolar macrophages (hematoxylin-eosin, 200×) (Slide courtesy Alberto Cavazza, MD)

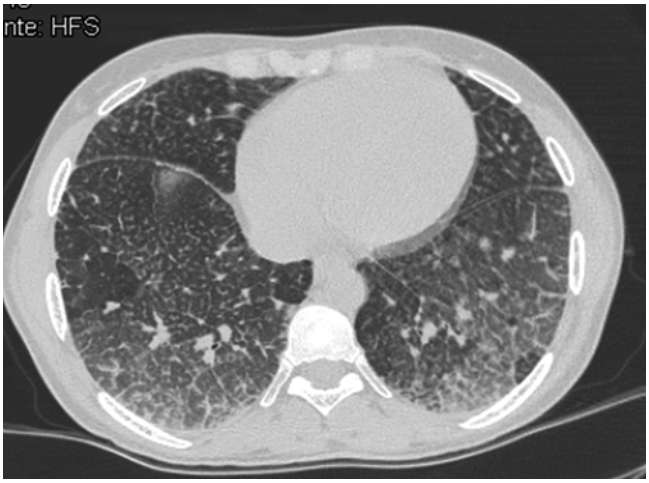

Fig. 36.5 Type B Niemann-Pick disease. Transverse CT scan of mid-lung zones in a 33-year-old woman shows severe interstitial changes. Note the presence of ground-glass opacities and the intermixed thickened interlobular septa and intralobular lines in some areas; these findings are suggestive of the "crazy paving" sign

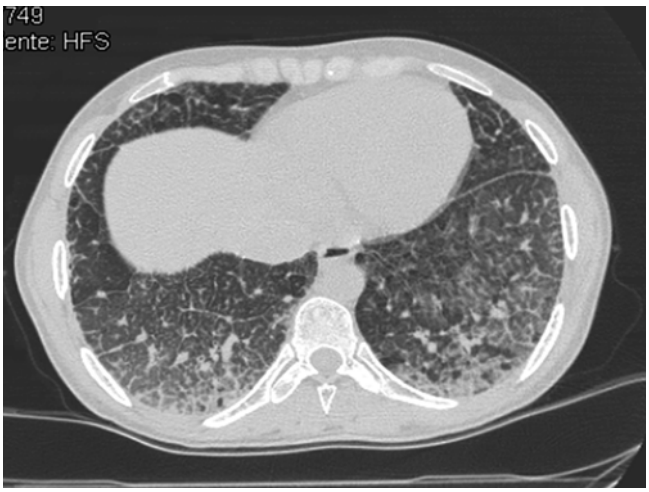

Fig. 36.6 Same patient as in figure 36.5. CT scan shows dense ground-glass opacities and thickened interlobular and intralobular septa "crazy paving"

test, which commonly shows a mild restrictive defect with minimal alteration of the diffusing capacity for carbon monoxide, do not appear to correlate with diseased extension on HRCT [45]. Improvement of endogenous lipid pneumonia has been reported with whole lung lavage [46]. A first product, miglustat, has been granted marketing authorization in Europe and several other countries for specific treatment of the neurological manifestations.

Fabry's Disease

Fabry's disease is an X-linked inborn error of glycosphingolipid catabolism, resulting from a deficient lysosomal α-galactosidase A activity, and characterized by an abnormal accumulation of the glycosphingolipid ceramide trihexoside in vascular smooth muscle throughout the body, particularly in vessels of the skin, kidneys, heart, pulmonary vascular and neurological system [48]. It begins in childhood with a median age of survival of 55 years, although adult patients with less pronounced disease can survive to older ages and be discovered because of cardiac involvement causing a cardiomyopathy [49]. Pulmonary involvement – in the form of diffuse alveolar hemorrhage associated with renal failure (pulmonary renal syndrome) – has occasionally been reported [50]. Conversely, airway obstruction manifesting with dyspnea, cough and wheezing and caused by deposition of glycosphingolipid in the cells lining small airways is a common finding in Fabry's disease

[51]. Previously a universally fatal disease, the recent development of human recombinant α-galactosidase A has been shown to reverse the clinical manifestations of the disease [52].

Lysinuric Protein Intolerance

Lysinuric protein intolerance is an autosomal recessive disease characterized by defective transport of lysine, arginine, and ornithine with excessive loss of proteins in the urine [53]. Lysinuric protein intolerance is caused by mutations in the solute carrier family 7A member 7 (SLC7A7) gene on 14q11.2, which encodes y^+ LAT-1 protein, the catalytic light chain subunit of a complex belonging to the heterodimeric amino acid transporter family. Mutations within SLC7A7 – mainly in the form of single-base substitutions or small deletions – have been identified in all but one individuals with lysinuric protein intolerance [54]. Initially described in Finland, lysinuric protein intolerance is a rare disease with fewer than 100 cases reported. Affected individuals demonstrate failure to thrive, growth retardation, hepatosplenomegaly, hypertonicity, and osteoporosis. Pulmonary involvement ranges from asymptomatic interstitial abnormalities to acute and life-threatening acute respiratory failure due to either alveolar hemorrhage or alveolar proteinosis – the latter being the most commonly observed interstitial lung disease [55]. Typically, in alveolar proteinosis the alveolar spaces are invaded by foamy macrophages filled with proteinaceous material, with chest radiograph revealing diffuse alveolar infiltrates. HRCT shows a characteristic pattern of ground glass opacities superimposed over a pattern of fine overlapping lines forming irregular polygonal shapes ("crazy paving" pattern). Similar to other forms of alveolar proteinosis, the treatment of choice is whole-lung lavage [56].

Familial Hypocalciuric Hypercalcemia

Familial hypocalciuric hypercalcemia is a rare autosomal dominant disorder with variable penetrance, characterized by familial hypercalcemia with hypocalciuria, granulocyte dysfunction, and interstitial lung disease (ILD) [57]. Familial hypocalciuric hypercalcemia is caused by inactivating mutations in the calcium sensing receptor gene leading to a calcium-hyposensitivity, compensatory hypercalcaemia – in order to obtain intracellular response despite inactive receptors – and hypocalciuria. The low urine calcium distinguishes familial hypocalciuric hypercalcemia from primary hyperparathyroidism, in which urine calcium excretion is increased. Lung involvement consists of a granulomatous disease, with foreign body giant cells and mononuclear cells infiltrating the alveolar interstitium. There are, however, no well-formed, circumscribed granulomas as observed in sarcoidosis or berylliosis. In addition, contrary to sarcoidosis and berylliosis, urine calcium is normal or low, and the level of 1,25-dihydroxyvitamin D3 is within normal limits. In general, familial hypocalciuric hypercalcemia is a benign condition that does not require treatment. As such, the main argument for establishing the diagnosis is to avoid unnecessary and futile parathyroidectomy. However, in chronic severe cases, lung fibrosis and honeycomb changes may lead to respiratory failure, thus reducing life expectancy. Chondrocalcinosis and acute pancreatitis have also been reported [58, 59]. The third feature of familial hypocalciuric hypercalcemia is granulocyte dysfunction due to a myeloperoxidase deficiency and reduced antistaphylococcal killing [60].

Neurofibromatosis Type 1

Neurofibromatosis 1 (NF1), previously known as von Recklinghausen's disease, is a systemic disorder affecting approximately 1 of 3,500 persons worldwide and caused by loss-of-function in the *NF1* gene (17q11.2) that encodes the tumor suppressor protein neurofibromin [61]. Despite its inheritance pattern – autosomal dominant – as many as 50 % of cases are spontaneous, that is caused by a *de novo NF1* mutation. NF1 is recognized by the appearance of multiple (>6) *café-au-lait* spots, axillary and inguinal freckling, optic gliomas, osseous lesions and cutaneous neurofibromas; internal neurofibromatous tumors are most commonly found in the central nervous system [62]. In addition, Lisch nodules, pigmented hamartomatous nodular aggregates of dendritic melanocytes affecting the iris, are present in over 90 % of patients. The spectrum of clinical phenotypes and their development, severity, and prognosis is large and is thought to result from the cross talk between numerous cell types, cell signaling networks, and cell-extracellular matrix interactions. At one end of this spectrum the lifetime risk of malignant tumors arising from peripheral nerves, which is estimated to be 10–13 % [63].

Interstitial lung disease, which usually appears between the ages of 35 and 60 years, complicates 6–12 % of cases [64]. The chest X-ray typically demonstrates – alone or in combination – lower zone (usually symmetrical) reticulonodular infiltrates and bullous changes (usually asymmetrical) in the upper zones [65]. HRCT reveals bibasilar reticular changes, ground glass opacities, upper lobe predominant small cysts and bullous changes [66]. Thin-walled bullae are present in almost all patients with ILD, although they may be seen in isolation. Histologically, alveolar septal fibrosis represents the major change, while an alveolitic process consisting of a mononuclear cell infiltration may be observed in earlier disease [67]. Functionally,

NF1-associated ILD is characterized by the gradual appearance and slow progression of a mixed obstructive and restrictive ventilatory defect. NF1-associated ILD is often progressive and may lead to pulmonary hypertension and right heart failure [68]. Rarer pulmonary complications of NF1 include large-airway obstruction, mediastinal, bronchial or intraparenchymal neurofibromas (leading to diaphragmatic paralysis), scar carcinoma complicating fibrotic lung disease, primary lung cancer developing in the walls of emphysematous cysts, and pneumothorax [69–71]. The pathogenesis of the ILD in NF1 is unknown and no effective therapies are currently available.

Surfactant Dysfunction Disorders

Surfactant dysfunction disorders are caused by mutations within genes encoding proteins needed for normal function and metabolism of surfactant, a mixture of phospholipids and proteins synthesized, packaged, and secreted by alveolar type II cells that lowers surface tension and prevents atelectasis at end-expiration. While rare, these disorders are associated with considerable pulmonary morbidity and mortality.

Surfactant Protein B (SFTPB) Deficiency

Surfactant protein B (SFTPB) deficiency is a rare autosomal recessive disease responsible for rapidly progressive neonatal respiratory distress syndrome [72]. Over 40 loss-of-function mutations within *SFTPB* gene that result in partial to complete absence of SP-B protein have been identified thus far. The most common one – a GAA substitution for C at genomic position 1,549 in codon 121 (the "121ins2" mutation), which accounts for approximately 70 % of cases of SFTPB deficiency – results in an unstable transcript and consequent absence of pro- and mature SFTPB protein [73]. The absence of SFTPB, in turn, leads to abnormal surfactant composition, decreased surfactant function, and structural disruption of lamellar bodies. Accordingly, SFTPB deficiency is characterized histologically by the accumulation of granular, eosinophilic, periodic acid-Schiff-positive, lipoproteinaceous material in the alveolar spaces, which often contains desquamated alveolar type II cells and foamy alveolar macrophages.

Clinical estimates suggest an incidence of 1 per million live births. Most infants with SFTPB deficiency present within hours of birth with respiratory failure requiring mechanical ventilation. Chest radiograph and HRCT appearance mimics 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 and, with rare exceptions, all patients succumb without lung transplantation. Children with mutations that allow for partial expression of the SFTPB protein appear to survive longer and go on to develop a chronic ILD [74].

Surfactant Protein C (SFTPC) Deficiency

Surfactant protein C (SFTPC) deficiency is a rare disorder originally described in an infant with nonspecific interstitial pneumonia (NSIP) whose mother had desquamative interstitial pneumonia. Both carried an heterozygous guanine to adenine substitution leading to skipping of exon 4 and deletion of 37 amino acids [2]. A large five generation kindred was later described with 14 affected family members, including four adults with surgical lung biopsy evidence of UIP and three children with NSIP, all carrying a rare heterozygous missense mutation substituting a polar residue (glutamine) for a neutral one (leucine) predicted to hinder processing of SP-C precursor protein [1]. Over 35 dominantly expressed mutations within *SFTPC* gene have been identified, half of which arise spontaneously, thus resulting in sporadic disease, whereas the remaining are inherited. The most common mutation, a T to C transition at genomic position 1,295, results in a threonine substitution for isoleucine in codon 73 (I73T), and accounts for a quarter of cases [75].

The pathophysiology of lung disease due to *SFTPC* mutations is complex and is thought to be related to aberrant surfactant protein folding, decreased endogenous SP-C secretion, endoplasmic reticulum stress and apoptosis of alveolar type II cells [76]. The age of onset and severity of disease are highly variable, ranging from fatal respiratory distress in infants to pulmonary fibrosis in older adults. In a recent study from the Netherlands *SFTPC* mutations accounted for as many as 25 % of familial pulmonary fibrosis kindreds [77]. Conversely, mutations within *SFTPC* are rarely associated with sporadic forms of pulmonary fibrosis [78]. Whether the nature and location of *SFTPC* mutations impact on 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]. The variability in the natural history of the disease precludes accurate assessment of prognosis for the individual patient and complicates interpretation of potential drug therapies.

Adenosine Triphosphate Binding Cassette Family Member 3 (ABCA3) Deficiency

The membrane transporter, member A3 of the Adenosine Triphosphate Binding Cassette family (ABCA3) facilitates the translocation into lysosomally-derived organelles called *lamellar bodies* of phospholipids for the production of surfactant in type II epithelial cells. Mutations in the gene encoding member A3 of the Adenosine Triphosphate

Table 36.1 Surfactant dysfunction disorders

Disease	SFTPB deficiency	SFTPC deficiency	ABCA3 deficiency	Brain-Thyroid-Lung syndrome
Locus	*SFTPB*	*SFTPC*	*ABCA3*	*NKX2.1*
Chromosome	2p11.2 s	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

Table 36.2 Other rare lung diseases of genetic origin

Alpha-1 antitrypsin deficiency
Birt-Hogg-Dube
Bronchopulmonary dysplasia
Cystic fibrosis
Ehlers-Danlos syndrome
Familial pulmonary arterial hypertension
Familial sarcoidosis
Hereditary hemorrhagic telangiectasia
Idiopathic pulmonary hemosiderosis
Kartagener syndrome
Marfan's syndrome
Primary ciliary dyskinesia
Primary immunodeficiency
Pulmonary alveolar proteinosis
Pulmonary alveolar microlithiasis
Familial systemic sclerosis
Tuberous sclerosis and lymphangioleiomyomatosis

Binding Cassette family may cause severe neonatal lung disease. In fact, similar to SP-B deficient infants, affected infants may present with severe respiratory distress syndrome that is progressive and refractory to all medical therapies [79]. However, older children and even young adults may present symptoms and signs of ILD without history of neonatal lung disease [80]. In addition, the family history is usually negative as the disease is inherited in an autosomal recessive fashion.

NK2 Homeobox 1/Thyroid Transcription Factor 1 (NKX2-1/TITF1) Mutations

NKX2-1 is a critical regulator of the expression of multiple surfactant-related genes. Deletions of or complete loss-of-function mutations on one copy (haploinsufficiency) of the NKX2.1 gene can result in severe respiratory distress syndrome and ILD [81]. 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 member A3 of the Adenosine Triphosphate Binding Cassette family, below a critical level. The incidence and prevalence of lung disease due to NKX2.1 haploinsufficiency are unknown. The gene is expressed in the thyroid gland and the central nervous system. As such, affected patients may have symptoms and signs related to those organ systems, e.g., hypothyroidism, muscular hypotonia, developmental delay, choreoathetosis as well as infant respiratory distress syndrome (most commonly) or chronic interstitial lung disease ("Brain-Thyroid-Lung syndrome") [82]. Irrespective of the gene involved, lung histology findings in surfactant dysfunction disorders are similar and include prominent alveolar type II epithelial cells hyperplasia, thickening of the interstitium with mesenchymal cells, and foamy macrophages and variable amounts of granular, eosinophilic proteinaceous material within the air spaces [83]. To date, no specific therapies for surfactant dysfunction disorders have been demonstrated to be effective. Features of surfactant dysfunction disorders are summarized in Table 36.1.

Other rare lung diseases of genetic origin are listed in Table 36.2.

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 36.3), specific histopathologic and radiographic features (Table 36.4), 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

Table 36.3 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 disease)	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 haemorrhage	Cardiac dysfunction	Angiokeratoma	
		Pneumothorax	Strokes	Corneal and lenticular opacities	
		Recurrent lung infections		Hypohidrosis.	
Lysinuric protein intolerance	Infancy-to-childhood	Interstitial lung disease	Growth retardation Hepatosplenomegaly Hypertonicity	Vomiting and diarrhoea on protein-rich diet	Increased urinary excretion and low plasma levels of lysine, arginine and ornithine
		Alveolar proteinosis	Osteoporosis	Hyperammonemia	
		Alveolar haemorrhage		Alopecia	
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 36.1

Table 36.4 Radiographic patterns of lung involvement on high-resolution computed tomography

Disease	Radiographic pattern
Hermansky-Pudlak syndrome	Diffuse, peripheral reticulation; subpleural cysts; ground glass opacitie, peribronchovascular thickening; bronchiectasis
Dyskeratosis congenita	Subpleural bibasal honeycombing, traction bronchiectasis, reticular opacities
Gaucher's disease	Reticular changes, ground glass opacities
Niemann-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

expected to identify markers of disease, pathways of disease regulation, and novel potential targets for therapeutic intervention. To this end, international collaboration – which allows collecting sufficiently large cohorts of patients with specific entities in order to perform proper therapeutic trials – is essential. Hopefully, this will help to reduce the still considerable morbidity and mortality associated with these disorders.

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Index

A
AAT deficiency. *See* Alpha-1 antitrypsin (AAT) deficiency
Abdominopelvic lymphatic disease, 278–279
ABPA. *See* Allergic bronchopulmonary aspergillosis (ABPA)
Accelerated pulmonary fibrosis, 561
ACIF. *See* Airway-centered interstitial fibrosis (ACIF)
Acute eosinophilic pneumonia (AEP), 553, 560, 562
Acute fibrinous and organizing pneumonia (AFOP), 374–375, 561
Acute interstitial pneumonia (AIP)
  clinical course, 352
  diagnostic evaluation, 351
  diffuse bilateral ground glass opacifications, 349, 350
  diffuse bilateral infiltrates without focal consolidation, 349, 350
  epidemiology, 350–351
  histopathology, 351–352
  history and definition, 350
  idiopathic, 171, 522
  pathophysiology, 352
  presentation, 351
  radiology, 351
  transthoracic echocardiogram, 349
  treatment, 352–353
Acute lupus pneumonitis (ALP)
  bronchoalveolar lavage, 393
  hemoptysis, 391
  HRCT, 391, 393
  LE cells, 391–392
  treatment, 393–394
Acute respiratory distress syndrome (ARDS)
  American European Consensus Conference, 171
  diffuse alveolar hemorrhage, 159
  histology, 171
  mortality, 171
  risk factors, 171
Adenosine triphosphate binding cassette family (ABCA3) deficiency, 604–605
ADPKD. *See* Autosomal dominant polycystic kidney disease (ADPKD)
Adult respiratory distress syndrome (ARDS)
  acute life-threatening reactions, 553–555
  acute vasculopathy, 565–566
  AEP, 560, 562
  APT, 561
  BAL, 557
  chemotherapy lung, 556
  diagnosis, 553
  DIPE, 553, 556
  OP, 560
  prevalence, 395
  pulmonary edema, 553, 556
  salicylate, 556
  TRALI, 557–558
AEP. *See* Acute eosinophilic pneumonia (AEP)
AFOP. *See* Acute fibrinous and organizing pneumonia (AFOP)
AIP. *See* Acute interstitial pneumonia (AIP)
Airway-centered interstitial fibrosis (ACIF), 20, 24, 25
Allergic bronchopulmonary aspergillosis (ABPA)
  A. fumigatus mediators and antigens, 56
  Aspergillus organisms, 54
  asthma and CF, 53
  B-cell response, 56–57
  bronchiectasis, 59, 66
  corticosteroids and itraconazole, 67
  description, 53
  diagnostic criteria, 243
  differential diagnosis (*see* Differential diagnosis, ABPA)
  environmental AF, 67
  eosinophil proteases and proteins, 56
  epidemiology, 53–54
  fumigatus, 61
  genetic factors, 55
  pathogenesis, 54–55
  pathophysiology, 54–55
  sero-positive, 66, 67
  stages, 63
  Th2-CD4^{+} T cell response, 56
  tissue damage, 57
  treatment (*see* Treatment, ABPA)
  without bronchiectasis, 66
Allogeneic hematopoietic stem cell transplantation (HSCT)
  BOS (*see* Bronchiolitis obliterans syndrome (BOS))
  chronic lung GVHD, 519
  CTD, 524
  high-dose steroids, 524
  IPS, 522
  myeloablative, 518
  OP, 522–523
  procedures, 518
  radiological signs, ILD, 524
Allogeneic HSCT. *See* Allogeneic hematopoietic stem cell transplantation (HSCT)
ALP. *See* Acute lupus pneumonitis (ALP)
Alpha-1 antitrypsin (AAT) deficiency, 37
Alveolar hemorrhage. *See* Diffuse alveolar hemorrhage (DAH)
Amiodarone pulmonary toxicity (APT), 541, 561–562, 570
Amyloid deposition
  AA, 96
  AL, 98
  clinical phenotypes, 91
  diffusion, 101
  laryngeal amyloidosis, 100–101
  mediastinal and Hilar amyloid lymphadenopathy, 102
  parenchymal pulmonary amyloidosis, 101–102
  plasmacytoma, 100

V. Cottin et al. (eds.), *Orphan Lung Diseases: A Clinical Guide to Rare Lung Disease*,
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Amyloid deposition (*cont.*)
radiologic appearance, 94
respiratory tract, 100
Sjogrens disease, 102
tracheobronchial amyloidosis, 101
treatment, 103–105
Amyloidosis
amyloidogenic protein, 91
classification, 91, 92
clinical phenotypes, 91
deposition (*see* Amyloid deposition)
description, 91
diagnosis and evaluation (*see* Diagnosis, amyloidosis)
fibrils production, 91, 105
heterogeneity, 91
heterogenous disease, 105
polypeptide chain, 91
respiratory diseases (*see* Respiratory diseases)
respiratory symptoms, woman, 105–106
SAP, 91
types, 92
ANCA-associated small vessel vasculitis
granulomatosis with polyangiitis, 161–162
microscopic polyangiitis, 161
Ankylosing spondylitis, 80
Anti-basement membrane antibody disease, 164–165
Anticoagulation
aneurysm, 185
immunosuppressive treatments, 185–186
inflammatory, 185
PAA, 184
vitamin K antagonists, 168
Anti-Jo1 antibody, 407
Anti-lysosomal membrane protein 2 (antiLAMP2), 130
Anti-myeloperoxidase (MPO)
ANCA, 113–114, 120, 130
antiPR3, 148
CSS patients, 113
GPA, 130, 133, 139, 148
HLA-DQ, 129
IgE titers, 117
microscopic polyangiitis-type, 129
P-ANCA, 118, 130
vasculitis, 130
Anti-neutrophil cytoplasm antibodies (ANCA)
anti-MPO, 113, 118
CSS, 113
GPA, 127, 161–162
initial symptoms, CSS, 115
kidney involvement, 177
MPA, 161
PR3-ANCAs, 83–84, 130, 140
relapse, 148
renal manifestations, 117
vasculitides, 120, 129, 146
Antinuclear antibodies (ANA), 380
Anti-oestrogen therapy, 280
Anti-phospholipid antibody syndrome (APLAS), 159, 163–164
AntiPR3 ANCA
alterations and maturation, 130
cANCA titers, 142
murine models, 130
PR3, 130
vasculitis, 130
Anti-streptolysin O test, 160
APT. *See* Amiodarone pulmonary toxicity (APT)
ARDS. *See* Acute respiratory distress syndrome (ARDS)
Arteriovenous malformations (AVMs). *See* Pulmonary AVMs
Asbestosis
alveolar macrophages, 484
BAL cytospin, 486, 487
classification, 484
diagnosis, 484, 486
HRCT scan, 484, 486
UIP pattern, 320
Ascaris pneumonia, 242
Asherson's syndrome, 163–164
Aspergillus fumigatus (AF), 53
Ataxia telangiectasia, 38
Autoimmune PAP
anti-GM-CSF antibodies, 287
biological exams, 287–288
bronchoalveolar lavage fluids, 287
chest CT scan, 286–287
clinical presentation, 286
epidemiology, 286
GM-CSF supplemental therapy, 288–289
open-lung biopsy, 288
prognosis and evolution, 288
pulmonary function tests and exercise capacity, 288
rituximab and plasmapheresis, 289
therapy, 288
whole-lung lavages, 288
Autosomal dominant polycystic kidney disease (ADPKD), 35, 37

B

BAL. *See* Bronchoalveolar lavage (BAL)
Barry–Perkins–Young syndrome, 34–35
B-cell non-Hodgkin lymphomas (NHL), 499
Behçet's disease (BD)
clinical features, 183
diagnostic criteria, 183
differential diagnosis, 185
epidemiology, 182
imaging studies, 184–185
laboratory findings, 184
parenchymal manifestations, 182
pathogenesis, 182–183
prognosis, 186
pulmonary artery aneurysm, 183–184
pulmonary parenchymal involvement, 184
therapeutic management, 185–186
vasculitis, 182
venous/arterial thrombosis, 182
Beryllium-lymphocyte proliferation test (Be-LPT)
bronchoalveolar lavage cells, 477, 478
cell cultures, 477–478
sensitivity, 478
urine and tissue samples, 479
Birmingham vasculitis activity score (BVAS), 143, 144
Birt–Hogg–Dubé syndrome. *See* Folliculin gene-associated syndrome (FLCN)
Bland pulmonary hemorrhage
etiologies (*see* Etiology, bland pulmonary hemorrhage)
histology, 166
Blood hypereosinophilia, 117
BOOP. *See* Bronchiolitis obliterans with organizing pneumonia (BOOP)
Borderline benign tumors, 590
BOS. *See* Bronchiolitis obliterans syndrome (BOS)
Brachmann–de Lange syndrome, 80

Bronchiolitis, adults
airways and respiratory portion, 17, 18
clinical syndromes, 17, 18, 23–25
constrictive bronchiolitis (*see* Constrictive bronchiolitis)
diagnosis, 21–23
epidemiology, 17
proliferative bronchiolitis, 20
treatment, 25
Bronchiolitis obliterans syndrome (BOS)
diagnosis, 519–521
incidence, 519
management, 521
physiopathology, 519
risk factors, 519
Bronchiolitis obliterans with organizing pneumonia (BOOP)
description, 363
flock, 483
GVHD, 519
hard metal lung, 482
HSCT, 523
LIP, 396
Bronchoalveolar lavage (BAL)
AIP, 351
Be-LPT, 477
bronchoscopy, 438
CD8+ lymphocytes, 497
CPFE, 337
CSS, 118
cytokines and osteopontin, 438
cytological analysis, 299
diagnosis, 511
double-contoured histiocytes, 221
ECD lung involvement, 220
ELP, 298, 299, 301
eosinophilic pneumonia, 231
flow-cytometry, 499
GPA, 140
HP, 460
IAEP, 233
and ICEP, 231
lymphocytes, 365, 374
lymphocytosis, 374
macroscopic observation, 220
microliths, 312
neutrophilia and extensive SSc-ILD, 384
Niemann-Pick cells, 601
optical microscopy analysis, 299, 301
PAP, 287
PLCH, 444
scanning/transmission electron microscopy, 484
Sjögren's syndrome, 401
SSc-ILD, 384–385
and TBB, 369
T-cell receptor repertoire and clonotype, 228
and transbronchial biopsy, 353, 511
ultrastructural analysis, 287
Bronchocentric granulomatosis, 245

C

Cancer mimics
bronchioloalveolar carcinoma, 582–583
cavitation, 586
EHE, 584–585
hyalinising granuloma, 589–590
IMT, 587–589
intrathoracic pseudotumors, 587
LYG, 585
lymphangitic carcinomatosis, 584
MCLD, 586
organising pneumonia, 581–582
PPL, 583–584
pulmonary hypertension, 586–587
sclerosing mediastinitis, 589
sugar tumor, 590
Cardiac MRI (CMRI), 117, 118
Castleman's disease (CD)
anti CD-20 monoclonal antibodies, 497–498
axillary nodes, 496
bronchoscopy, 497
hyaline-vascular (HV), 497
interleukin-6 (IL-6), 497, 498
multicentric (M-CD), 497
plasma cells, 497
Cellular bronchiolitis, 19, 458
CFTR. *See* Cystic fibrosis transmembrane conductance regulator (CFTR)
Chronic beryllium disease (CBD)
Be-LPT (*see* Beryllium-lymphocyte proliferation test (Be-LPT))
beryllium oxide, 479
cell cultures, 477–478
copper-beryllium alloys, 479
description, 473, 474
diagnosis, 476–477
epidemiology, 474–475
genetics, 475
granulomas disorders, 475–476
immunopathogenesis and pathology, 475
neutron moderators, 479
nonoccupational cases, 474
prevention, 480–481
radiographic and laboratory differences, sarcoidosis, 476
toxic compounds and bioaerosols, 473
treatment and monitoring, 480
urine and tissue samples, 479
workplaces, components and products, 480
Chronic bronchiolitis. *See* Bronchiolitis, adults
Chronic graft-*versus* host disease (cGVHD)
autoimmune disorders, 524
BOS (*see* Bronchiolitis obliterans syndrome (BOS))
hypothesis, 523
OP, 523
tissue destruction, 518
Chronic granulomatous disease (CGD), 38
Chronic large-vessel granulomatous vasculitis, 177
Chronic obstructive pulmonary disease (COPD)
"emphysema-like" lesions, 328
LCs, 437–438
respiratory bronchioles, 353
tracheomalacia, 79
Churg–Strauss syndrome (CSS)
abdominal angiography, 118
after heart transplantation, 123
ANCA, 118
blood hypereosinophilia, 117
bronchoalveolar lavage fluid, 118
cardiac abnormalities, 118
cardiomyopathy, 122
cardiopulmonary resuscitation and adrenaline, 122
CMRI, 118
2D and 3D cardiac MRI, 122
diagnosis (*see* Diagnosis)

Churg–Strauss syndrome (CSS) (*cont.*)
EGPA, 113
Enterobacter aerogenes, 123
eosinophilia, 118
epidemiology (*see* Epidemiology, CSS)
gastrointestinal involvement, 116
general symptoms, 115
heart manifestations, 116–117
heterogeneity, 123
history of asthma, 122
IgE, 118
imaging techniques, 118
inflammation, 117–118
initial symptoms, 115
neurological manifestations, 116
organ locations, 117
pathophysiology, 113–114
prognosis and outcomes, 120–121
pulmonary manifestations, 115–116
renal manifestations, 117
respiratory tract, 115
rheumatoid factor-positivity, 118
rheumatological manifestations, 117
skin manifestations, 116
thoracic computed-tomography, 115, 116
treatment, 113, 121–122
vessel vasculitis, 113
Cigarette smoking
COPD and bronchogenic carcinoma, 435, 453
ILDs, 435, 436
PLCH, 435
respiratory bronchiolitis, 435–436
Clinical syndromes of bronchiolitis
airway-centered interstitial fibrosis, 24
connective tissue diseases, 24
cryptogenic adult bronchiolitis, 24
diffuse panbronchiolitis, 24–25
drug-induced, 24
hematopoietic stem cell transplantation, 24
idiopathic clinicopathologic syndromes, 23
infectious, 23
inhalational lung injury, 23
organic and mineral dusts, 23
organ transplantation, 24
volatile flavoring agents, 23
Collagen disorders, 38–39
Combined pulmonary fibrosis and emphysema (CPFE)
biology, 336–337
centrilobular emphysema and usual interstitial pneumonia, 333, 334
at chest CT with, 332, 333, 335
clinical and functional characteristics, 328
clinical manifestations, 331
comorbidities and complications, 341
computed tomography characteristics, 333
description, 327
diagnosis, 336
and emphysema syndrome, 532–533
function and physiology, 331–332
imaging patterns, 333–334
lung cancer, 339–341
mortality, 338–339
paraseptal emphysema, 334
pathology, 337–338
PH, 339, 342
“possible honeycombing”, 334
with predominantly paraseptal emphysema, 333, 335
pulmonary fibrosis, 341, 342
thick-walled large cysts, 333, 336
Common variable immunodeficiency (CVID)
complement deficiency, 38
immunodeficiencies, 37
immunoglobulin substitution therapy, 45
Connective tissue disease (CTD)
ANA positivity, 422
anti-CCP positivity, 422–423
autoantibodies, 421, 422, 428
AZA, 431
biologic agents, 431
complementary modalities, 431
CS and CYC, 430
cyclosporine and tacrolimus, 431
demographics, 427
description, 391
diagnosis, 420–421
histopathology, 429
HRCT, 428–429
hypertension and hypothyroidism, 419
idiopathic interstitial pneumonia, 421
immunomodulatory therapy, 429–430
inflammatory arthritis, 427
MCTD, 409–410
mechanic’s hands, 422, 427, 428
methotrexate (MTX), 431
mycophenolate mofetil (MMF), 430
non-specific symptoms, 428
palmar telangiectasia, 427, 428
patients with pre-existing, 421
polymyositis and dermatomyositis, 406–409
pulmonary manifestations, 419–420
RA, 396–401
Raynaud’s phenomenon, 422, 427
and rheumatologic disorders, 419, 420
SLE, 391–396
SS, 401–406
standardized tools, 427
UCTD, 423–427
Constrictive bronchiolitis
ACIF, 20
airway lumen, 17, 19
cellular, 19
diffuse, 20
follicular, 19
respiratory, 20
treatment, 25
CPFE. *See* Combined pulmonary fibrosis and emphysema (CPFE)
“Cryptogenic fibrosing alveolitis”, 327
Cryptogenic organizing pneumonia (COP)
AFOP, 375
BAL and TBB, 369
cause of relapses, 373
corticosteroid treatment, 372
description, 363
diagnosis, 369
erythromycin and clarithromycin, 373
CTD. *See* Connective tissue disease (CTD)
CVID. *See* Common variable immunodeficiency (CVID)
Cystic fibrosis (CF)
and asthmatics, 62–63
CFTR gene mutations, 31–32
incidence, 31
morbidity and mortality, 47
omalizumab, monoclonal antibody, 66
pro-Th2 chemokines, ABPA, 56

respiratory cilia beat, 31
sweat test, 32
Cystic fibrosis transmembrane conductance regulator (CFTR), 55, 598

D
DAH. *See* Diffuse alveolar hemorrhage (DAH)
DC. *See* Dyskeratosis congenita (DC)
Dermatopolymyositis, 406, 409, 411
Desquamative interstitial pneumonia (DIP). *See also* Respiratory bronchiolitis interstitial lung disease (RB-ILD)
clinical course, 356–357
description, 451
diagnosis, 356, 445, 448, 451–452
epidemiology, 30, 355, 437, 448, 451–452
histopathological findings, 356, 452
history and definition, 355
presentation, 355–356
prognosis and therapy, 453
radiological findings, 356, 452–453
treatment, 357
Diagnosis
amyloidosis
AL amyloid, 95
amyloid fibril deposition, 92
amyloidogenic protein production, 92
ATTR amyloid, 96
cardiac magnetic resonance imaging, 96
chronic pulmonary conditions, 92
Congo red staining, 93
CT and MRI, 95
extra-pulmonary systemic disease, 95
fatal lung haemorrhage, 92
formalin fixation, biopsy, 92
genetic variants, 94
heterogenous disease, 92
immunoglobulin gene rearrangement studies, 95
immunohistochemical stains, 93
NMIDD, 93–94
non-invasive diagnostic test, 96
patients with suspected amyloidosis, 95
plain radiography, 94
radiologic appearance, amyloid deposition, 94
risk of haemorrhage, 93
SAP scintigraphy, 95
subtypes, 93
tissue confirmation, 92, 93
two-dimensional Doppler echocardiography, 95–96
web-based repository, 94
bronchiolitis
chest imaging studies, 22–23
pulmonary function testing, 23
surgical lung biopsy, 21, 23
CSS
asthmatic patient, 118
criteria, 119
differential diagnosis, 120
histological findings, 118–119
skin, nerve and muscle biopsy, 118
DAH, 159–160
GPA
antiPR3 cANCA, 138
classification criteria, 138
clinical features, 138, 139
immunology, 139–140
laboratory investigations, 139
pathology, 140–141
radiology, endoscopy and non-biologic investigations, 140
renal biopsy, 138
severe anemia, female, 139
HP
bronchoalveolar lavage (BAL), 458, 460
clinical behavior and classification, 457–458
criteria, 461
GERM'O'P management, 462, 463
histologic features, 458–459
imaging features, 459–460
open-lung biopsy, 458
PFTs, 461
probability (%), 461, 462
serum antibodies, 460–461
significant predictors, 461
Differential diagnosis, ABPA
acute exacerbation of asthma, woman, 57–59
allergic aspergillus sinusitis, 63–64
aspergilloma and invasive aspergillosis, 64
asthmatics and CF patients, 62–63
asthma with fungal sensitisation, 63
chronic necrotising pulmonary aspergillosis, 64
clinical symptoms, 59
definition, 57
hypersensitivity pneumonitis, 64
pathology, 62
radiological patterns and pulmonary function tests, 59–61
skin tests and biological investigations, 61–62
Diffuse alveolar damage (DAD)
etiologies (*see* Etiology, DAD)
histology, 168–169
Diffuse alveolar hemorrhage (DAH)
BAL, 155
bland pulmonary hemorrhage (*see* Bland pulmonary hemorrhage)
bleeding, 562
brodifacoum, 562
clinical manifestations, 562
clinical presentation, 157–159
clinicians, 173
cocaine, 563
DAD (*see* Diffuse alveolar damage (DAD))
description, 155
diagnosis, 159–160, 394
differential diagnosis, 155
fluid silicone/hyaluronate, 563
Goodpasture, 565
hemoptysis, 562
pathogenesis, 394
progressive dyspnea, 155–157
progressive fatigue, 156–157
propythiouracil (PTU), 564–565
pulmonary capillaritis (*see* Pulmonary capillaritis)
risk factors, 563
treatment, 394–395
Diffuse bronchiectasis
collagen disorders, 38–39
diagnosis
characteristic features, 41–42
chest x-ray, 40
fibreoptic bronchoscopy, 41
fluid-filled bronchi, 40
HRCT, 41
patient, symptoms, 40
respiratory tract symptoms, 40
epidemiology, 30
genetic causes, 30
genetic predispositions, 39

Diffuse bronchiectasis (*cont.*)
idiopathic, 39
immunity, 37–38
innate immunity and ion-transport disorders, 47
mucociliary clearance (*see* Mucociliary clearance)
pathophysiology, 29–30
post-infectious, 29
treatment
airway clearance technique, 43–44
antibiotic therapies, 43
anti-inflammatory management, 44–45
gene and immune therapy, 45–46
infections, management, 44
surgery, 45
Diffuse panbronchiolitis, 20, 24–25
Diffuse pulmonary AVMs
description, 194
post-embolization, PaO_2, 195
unilateral/bilateral, 194
VMs, 195
Diffusing capacity for carbon monoxide (DLCO), 159, 167, 170, 207
DIP. *See* Desquamative interstitial pneumonia (DIP)
DIPE. *See* Drug-induced pulmonary edema (DIPE)
DLCO. *See* Diffusing capacity for carbon monoxide (DLCO)
Drug-induced pulmonary edema (DIPE), 553–554, 556
Drug-induced respiratory disease (DIRD)
accelerated pulmonary fibrosis, 561
acute infiltrative lung disease, 558
acute nonspecific-like interstitial pneumonitis, 558–559
amphetamine-like anorectics, 552
anaphylaxis, 566
angioedema, 566
APT, 561
ARDS (*see* Adult respiratory distress syndrome (ARDS))
bezoars and gossypibomas, 571
bronchospasm, 567–568
chest pain, 571
classic offenders, 541, 543
common inducers and patterns of involvement, 549–551
DAH, 562–565
diagnosis, 547–549
drug abuse and misuse, 541
drug families, 543–546
exacerbated pulmonary fibrosis, 565
gold and penicillamine, 552
granulomatous ILD, 559–560
'idiopathic', 572
life-threatening adverse effects, 541, 542
L-tryptophan, 552
mitomycin pneumonitis, 552
nonpulmonary disciplines, 572–574
orphan conditions, 541
peri-operative emergencies, 568–570
pleuroparenchymal fibroelastosis, 571
Pneumotox, 541, 549
pulmonary nodules and masses, 570–571
radiation, 571
rebound and recall phenomenon, 571
targeted agents, 543
TRALI, 557–558
Dyskeratosis congenita (DC), 599–600

E
ECD. *See* Erdheim-chester disease (ECD)
EHE. *See* Epithelioid hemangio-endothelioma (EHE)
Ehlers–Danlos syndrome, 39, 80, 264
ELISA. *See* Enzyme-linked immunosorbent assay (ELISA)
ELP. *See* Exogenous lipoid pneumonia (ELP)
Emphysema
CPFE (*see* Combined pulmonary fibrosis and emphysema (CPFE))
"cryptogenic fibrosing alveolitis", 327
etiological factors, 331
genetic predisposition, 328–329
measures and treatment, 341
systemic diseases, 329–331
tobacco smoking and male sex, 328
Endobronchial ultrasonography (EBUS), 75, 83–86, 511
Enzyme-linked immunosorbent assay (ELISA), 113, 127, 139, 140, 148, 160, 167
Eosinophilia-myalgia syndrome, 552
Eosinophilic granulomatosis with polyangiitis (EGPA)
Churg Strauss syndrome, 160
clinical features, 235
differential diagnosis, 237–238
history and nomenclature, 234–235
imaging, 235–236
laboratory studies, 236
pathogenesis, 236–237
pulmonary capillaritis, 166
treatment and prognosis, 239
Eosinophilic pneumonia
ABPA, 242–243
ascaris pneumonia, 242
biology, 244
bronchial hyperreactivity, 246
bronchocentric granulomatosis, 245
cationic proteins, 228
classification, eosinophilic lung diseases, 227
clinical presentation, 228–229
conspicuous eosinophils/ICEP, 246
corticosteroids, 228
Δdbl-GATA-1 transcription factor, 227
diagnostic criteria, 243–244
drug and toxic agents, 245–246
granulomatosis, polyangiitis, 234–239
historical perspective, 228
hypereosinophilic syndrome, 239–241
IAEP, 232–234
ICEP, 230–232
idiopathic hypereosinophilic obliterative bronchiolitis, 241
imaging, 244–245
intercellular signaling, 228
intracytoplasmic granules, 228
larva migrans syndrome, 242
Löffler's syndrome, 242
parasitic infestation and eosinophil leukocytes, 227
pathogenesis, 243
strongyloides stercoralis infection, 242
treatment, 245
tropical eosinophilia, 241–242
Epidemiology
Behçet's disease (BD), 182
CSS
incidence and prevalence, 114
triggering factors, 114–115
TA, 177
Epithelioid hemangio-endothelioma (EHE), 584–585
Erdheim-chester disease (ECD)
$BRAF^{V600E}$ mutation, 214
bronchoalveolar lavage (BAL), 220

clinical and radiological characteristics, 212, 213
comparison, LCH, 222
description, 211
double-contoured histiocytes, BAL fluid, 221
histologic and skeletal findings, 224
IFNα, 213
imaging features, 219, 220
imatinib mesylate, 213
PFT, 220
pulmonary involvement, 214–218
treatments, 213–214
Etiology
bland pulmonary hemorrhage
coagulopathy, 168
drugs and medications, 167–168
extremely severe cases, 168
idiopathic pulmonary hemosiderosis, 166–167
inhalation, 168
left ventricular dysfunction, 168
pulmonary veno-occlusive disease, 168
valvular heart disease, 168
DAD
acute exacerbation of interstitial lung disease, 170
acute interstitial pneumonia, 171
acute respiratory distress syndrome, 171–172
cocaine inhalation, 170
HSCT, 169–170
pulmonary capillaritis
alveolar damage, 165
antiphospholipid antibody syndrome, 163–164
Behçet's disease/syndrome, 165–166
causes, 166
cryoglobulinemia, 166
Goodpasture's syndrome, 164–165
granulomatosis with polyangiitis, 161–162
Henoch-Schönlein purpura, 165
isolation, 162–163
lung allograft rejection, 165
microscopic polyangiitis, 161
SLE and antiphospholipid syndromes, 165
systemic lupus erythematosus, 163
Ex Churg–Strauss syndrome. *See* Eosinophilic granulomatosis with polyangiitis (EGPA)
Exogenous lipoid pneumonia (ELP)
BAL, 298–299, 301
clinical manifestations, 297
description, 295
differential diagnosis, 301
epidemiology, 295–296
etiology and predisposing factors, 296–297
histopathology, 300–301
natural history and complications, 301
pathophysiology and histopathology, 296
radiological examinations, 298–300
treatment, 301–302

F

Fabry's disease, 602–603
Familial hypocalciuric hypercalcemia, 603
Fibrotic chronic HP, 469
FLCN. *See* Folliculin gene-associated syndrome (FLCN)
Flock worker`s disease
description, 483–484
diagnosis, 484
HRCT scan and NSIP, 484, 485
Follicular bronchiolitis, 19, 25, 261, 403, 499
Follicular lymphoma (FL), 503–504, 511
Folliculin gene-associated syndrome (FLCN)
colorectal polyps and carcinoma, 258
cutaneous manifestations, 254, 257–258
imaging, 256
novel non-eponymous terminology, 255
parotidal tumours, 258
pathology, 256–257
pulmonary manifestations, 254–256
renal manifestations, 258
renal tumours, 255
spontaneous pneumothorax, 258–259

G

Gastroesophageal reflux disease (GERD), 25, 75
Gaucher's disease, 600–601
Giant cell interstitial pneumonitis (GIP)
description, 481–482
diagnosis, 482
transbronchial biopsy and BAL cytology, 482, 483
Goodpasture's syndrome, 134, 160, 164–165
Granulocyte-macrophage colony-stimulating factor (GMCSF), 56
Granulomatosis with polyangiitis (GPA)
adults, 127
ANCA and cANCA, 127
autoimmune multisystem disease, 83
cardiac involvement, 136
clinical manifestations, 131
CNS manifestations, 134
constitutional symptoms, 131
diagnosis (*see* Diagnosis)
disease activity and prognosis, 142–143
ear, nose and throat manifestations, 131–132
epidemiology, 128–129
eye manifestations, 135–136
gastrointestinal manifestations, 136
gynecologic and obstetric manifestations, 137
historical overview, 127–128
kidney manifestations, 134
limited/localized *vs.* severe/diffuse/ systemic forms, 137
modalities of treatment, 127
pathogenesis, 130
patient's experience, 127
pediatric, 137–138
peripheral nervous system manifestations, 134
pulmonary function, 84
pulmonary manifestations, 132–134
relapse, 148–149
rituximab, 149
skin and oral mucosal manifestations, 135
spinal cord and cranial nerve involvement, 134–135
survival and causes of deaths, 148
therapeutic trials, 149
thyroid gland, 137
treatment (*see* Treatment, GPA)
urological manifestations, 134
venous thrombosis and vascular events, 137

H

Hard metal lungs
description, 481–482
diagnosis, GIP, 482, 483
giant cell pneumonitis, 482, 483

Hematological malignancies
allogeneic HSCT (*see* Allogeneic hematopoietic stem cell transplantation (HSCT))
description, 517
drugs, 517, 518
immunological causes, pneumonitis, 517–518
Hematopoietic stem cell transplantation (HSCT), 24, 169–170
Hepatopulmonary syndrome (HPS)
algorithm, diagnostic, 207, 208
arterial hypoxemia, 205
clinical features, 205
diagnostic criteria for, 201
DLCO, 207
indirect echocardiographic markers, 205
intrapulmonary vascular dilatation, 205
lung perfusion scanning with brain imaging, 206–207
MELD scale, 208–209
pathophysiology
bile duct ligation rat model, 203
clinical diagnosis of, 205
exhaled nitric oxide levels, 203
gas exchange, 202
genetic risk factors, 204
hypoxemia mechanism, 202–203
percutaneous liver biopsy, 205
TNFα levels, 204
type I and II dilatations, 202
pharmacologic treatment, 207
portal hypertension and hepatic dysfunction, 201
prevalence rates, 201, 202
prognosis, 209
recurrence, 207
treatment options, 207, 208
type I and II dilatations, 207
UNOS policy, 207–208
Hereditary hemorrhagic telangiectasia (HHT)
ACVRL1 mutation, 535
antibiotics for prophylaxis, 194
arteriovenous malformations, 534
characteristics, 534
children with, 194
clinical diagnostic criteria, 197
Endoglin/ACVRL1 genes, 191
follow-up after embolization, 194
genotype-phenotype correlation, 197
hemorrhagic complications, 192
idiopathic, 191
mucocutaneous telangiectasia, 197
Osler-Weber-Rendu disease, 196–197
paradoxical embolisation, thrombus, 193
pathogenesis, 197–198
preventative transcatheter embolotherapy, 193
screening and preventative therapy, 193
simple fistulas, 192
Hermansky–Pudlak syndrome (HPS), 597–599
HES. *See* Hypereosinophilic syndrome (HES)
High-grade primary large pulmonary B cell lymphomas, 504
High-resolution computed tomography (HRCT)
abnormalities, 380
alveolar hemorrhage, 156
ARDS, 351
BAL, 384–385
bronchiectasis, 41
clinical diagnosis, IPF, 323
description, 30
detecting symptomatic disease, 30
diagnostic sensitivity, 380
evaluation, 382–383
features, 316
FVC value, 383–384
ground-glass opacities, 316
HPS, 599
ICEP, 230
idiopathic NSIP, 382, 383
ILD, 428–429
“intermediate”, 386, 387
NSIP and UIP patterns, histology, 323
PFTs, 381, 382
PLCH, 441–443
radiologic patterns, interstitial lung diseases, 315, 316
SSc-ILD, 379, 382
traction bronchiectasis, 382, 383
UIP pattern, 316
Hilar amyloid lymphadenopathy, 102
HIV. *See* Human Immunodeficiency Virus (HIV)
Home-related HP, fungi
classic risk factors, 463
contamination, 463
environmental investigations, 463
farmer’s lung disease, 463
gravity culture technique, 467
low-energy housing, 463
microorganism cultures, 467
“smell tests”, 467
visual inspection, 467
HPS. *See* Hepatopulmonary syndrome (HPS); Hermansky–Pudlak syndrome (HPS)
HRCT. *See* High-resolution computed tomography (HRCT)
Hugues–Stovin syndrome, 183–185
Human Immunodeficiency Virus (HIV)
etiologies, 172
LIP, 498
plasmablastic pulmonary plasmacytoma, 502
systemic AA amyloidosis, 97
T-cell lymphomas, 508
Human leucocyte antigen (HLA)-DR, 55
Hypereosinophilic syndrome
clinical and imaging features, 240
laboratory studies, 240
pathogenensis, 239–240
treatment and prognosis, 240–241
Hypereosinophilic syndrome (HES), 120, 238–240
Hyper-IgE syndrome, 263
Hypersensitivity pneumonitis (HP)
allergic alveolitis, 457
anticipatable causes, 468
antigen(s) tracking and identification, 462
diagnosis
bronchoalveolar lavage (BAL), 458, 460
clinical behavior and classification, 457–458
criteria, 461
GERM’O’P management, 462, 463
histologic features, 458–459
imaging features, 459–460
open-lung biopsy, 458
PFTs, 461
probability (%), 461, 462
serum antibodies, 460–461
significant predictors, 461
fibrotic chronic HP, 469
fungi (*see* Home-related HP, fungi)

HP Study Group definition, 457
immunologic lung disease, 457
NHLBI/ORD workshop report, 457
non anticipatable causes, 469
NTM, 467
rare causes/etiological circumstances, 463–467
rare/novel causes, 468
Hypoxemia mechanism
anatomic intrapulmonary shunting, 203
non-vascular reasons, 202–203
type I diffuse intrapulmonary vascular dilatations, 203

I
ICEP. *See* Idiopathic chronic eosinophilic pneumonia (ICEP)
Idiopathic acute eosinophilic pneumonia (IAEP)
BAL, 233
clinical features, 232
diagnostic criteria, 232
imaging, 232–233
laboratory studies, 233
lung biopsy, 234
lung function tests, 233–234
treatment and prognosis, 234
Idiopathic bronchiectasis
characteristic features, 41–42
chest x-ray, 40
fibreoptic bronchoscopy, 41
fluid-filled bronchi, 40
HRCT, 41
patient, symptoms, 40
respiratory tract symptoms, 40
Idiopathic chronic eosinophilic pneumonia (ICEP)
BAL, 231
clinical features, 230
differential diagnosis, 231
imaging, 230
laboratory studies, 231
lung function tests, 231
treatment and prognosis, 231–232
Idiopathic giant trachea, 81
Idiopathic pneumonia syndrome (IPS), 522, 523
Idiopathic pulmonary fibrosis (IPF), 157, 170
Idiopathic pulmonary hemosiderosis (IPH), 166–167
Idiopathic subglottic stenosis (ISS), 74–76
Immunity disorders
ataxia telangiectasia, 38
CGD, 38
CVID, 37
innate immunodeficiency, 38
neutrophil function, 38
XLA, 37–38
Indium–tin oxide (ITO), 481
Inflammatory myofibroblastic tumor (IMT)
Anaplastic Lymphoma Kinase (ALK) gene, 588
clinical-radiological features, 588
description, 587
fibroblasts and myofibroblasts, 587
immunoglobulin (Ig) G4 expression, 587–588
prognosis, 588–589
treatment, 588
Interstitial lung diseases (ILDs)
chest HRCT (*see* High-resolution computed tomography (HRCT))
clinical entities, 315
UIP pattern (*see* Usual interstitial pneumonia (UIP) pattern)
Intrapulmonary lymph nodes, 493, 499
Intravascular large B-cell lymphoma
characteristics, 506
diagnosis, 504–505
neoplastic lymphoid cells, 504, 505
pleural effusion and parenchymal involvement, 504, 505
proliferation, 504
pulmonary arterial hypertension, 504
IPF. *See* Idiopathic pulmonary fibrosis (IPF)
IPH. *See* Idiopathic pulmonary hemosiderosis (IPH)
IPS. *See* Idiopathic pneumonia syndrome (IPS)
ITO. *See* Indium–tin oxide (ITO)

K
Kenny–Caffey syndrome, 80

L
LAM. *See* Lymphangioleiomyomatosis (LAM)
Langerhans cell histiocytosis
clinical features, 260
diagnosis and management, 261
imaging, 260–261
pathology, 260
Langerhans cell histiocytosis (LCH)
acute disseminated, 592
aggressive immunosuppressive therapy, 603
bone lesions evaluation, 439
comparison, ECD, 222
histiocytes, 213
pulmonary and/or multisystemic involvement, 446
Laryngeal amyloidosis, 100–101
Leukotriene receptor antagonists (LTRA), 560
Liebow's lymphomatoid granulomatosis, 141
LIP. *See* Lymphocytic interstitial pneumonia (LIP)
Liver VMs
Bevacizumab, 196
Doppler ultrasound, detection, 195
HOCF, 195
percutaneous hepatic artery embolization, 196
perioperative mortality, 196
surgical hepatic ligation, 196
symptomatic, 195
Löffler's syndrome, 242
LTRA. *See* Leukotriene receptor antagonists (LTRA)
Lung allograft rejection, 165
Lung biopsy
chronic bronchiolitis, adults, 23
histology of, 317–319
morphologic features, 318
PLCH, 444
prognostic and therapeutic consequences, 317
pulmonary pathologists, 317
TBLB, 319
Lung perfusion scanning, 206–207
LYG. *See* Lymphomatoid granulomatosis (LYG)
Lymphangioleiomyomatosis (LAM)
abdominal disease, 272
abdominopelvic lymphatic disease, 278–279
anti-oestrogen therapy, 280
asthma, treatment, 272
bronchodilators, 280
chest radiograph, 274
chronic respiratory disease, 277
chylous effusion and lung cysts, 272

Lymphangioleiomyomatosis (LAM) (*cont.*)
clinical features, 259
clinical scenarios, 273
CT scanning, 273
description, 271
European Respiratory Society diagnostic criteria, 274, 276
haemorrhage/chyle, 274, 275
imaging, 259–260
lung biopsy, 275
oxygen therapy, 281
parenchymal lung disease, 277
pathogenesis, 271–272
PH associated with, 533–534
pleural disease, 277
pregnancy, 279
prognosis, 277
pulmonary function testing, 274–275
pulmonary hypertension, 281
renal angiomyolipoma, 277–278
sporadic and TSC-LAM, 275
tuberous sclerosis, 279–280
VEGF-D, 276
video assisted thoracoscopic biopsy, 275
Lymphangitic carcinomatosis, 584
Lymphocytic bronchiolitis, 519–520
Lymphocytic interstitial pneumonia (LIP)
CT scan, 403
follicular bronchiolitis and BAL lymphocytosis, 398, 403
ground-glass attenuation, 498
HRCT, 428, 429
pleural effusion, 498
pulmonary cysts, 404
serum protein abnormality, 498
symptoms, 498
treatment, 403, 499
Lymphoid disorders
amyloidosis, 262
interstitial pneumonia, 261
nonamyloid immunoglobulin deposition disease, 262
pulmonary lymphoma, 261–262
Lymphomatoid granulomatosis (LYG)
chemokines, 507
chemotherapy, 585
distribution, 506
Epstein-Barr virus (EBV), 506, 507
haemoptysis, 506
hypereosinophilia, 585
lung nodules, 506
necrosis, 507
treatment, 512
waxing and waning, 506
Lymphoproliferative lung disorders
classification, 493–495
PPL (*see* Primary pulmonary lymphomas (PPL))
reactive pulmonary lymphoid hyperplasia, 496–499
secondary lymphomas, 512–513
Lysinuric protein intolerance, 291, 603
Lysosomal lipid storage disease
description, 600
Fabry's disease, 602–603
familial hypocalciuric hypercalcemia, 603
Gaucher's disease, 600–601
lysinuric protein intolerance, 603
NF1, 603–604
NPD, 601–602

M
Macrophage-derived chemokines (MDC), 56, 510
MALT lymphoma. *See* Mucosa-associated lymphoid tissue (MALT) lymphoma
Marfan syndrome, 39, 80, 81
MCLD. *See* Multiple cystic lung disease (MCLD)
Mesenchymal borderline disorders, 590–591
Microscopic polyangiitis (MPA), 161–164, 331
Mixed connective tissue disease (MCTD), 409–410, 421, 427
Model for end-stage liver disease (MELD), 208–209
Monomac syndrome, 291
Mounier–Kuhn syndrome, 39, 79–81
Mucociliary clearance
AAT deficiency, 37
ADPKD, 37
CF, 31–32
non-motile/'primary' cilia, 35
PCD (*see* Primary ciliary dyskinesia (PCD))
respiratory cilia, 31
Young's syndrome, 34–35
Mucocutaneous telangiectasia, 197
Mucosa-associated lymphoid tissue (MALT) lymphoma
air bronchogram, 583, 593
angiogram sign, 500
B cell, 499
bronchioloalveolar carcinoma, 582
characteristics, 501
chromosomal translocations, 584
cytogenetic features and molecular pathogenesis, 500–501
diagnosis, 511
Gougerot–Sjögren syndrome, 583
halo sign and peribronchovascular nodules, 501, 502
inflammatory processes, 500
medical thoracoscopic lung biopsy, 501, 503
NLH, 591
polyclonal lymphoproliferation to clonal disease, 102
pulmonary symptoms, 500
treatment, 512
Multiple cystic lung disease (MCLD)
benign uterine leiomyoma, 264
bulla and pneumatocele, 253
congenital cystic disorders, 264
cyst formation, mechanisms, 253, 265
definition, 586
diagnosis, 265, 266
Ehlers–Danlos syndrome, 264
and FLCN, 254–259
hyper-IgE syndrome, 263
interstitial lung diseases, 264
LAM, 259–260
langerhans cell histiocytosis, 260–261
lymphoid disorders, 261–262
malignancies, 264
mesenchymal cystic hamartomas, 264
metastases, sarcomas, 263
neurofibromatosis, 264
Pneumocystis jiroveci pneumonia, 263
posttraumatic pseudocysts, 264
progressive destruction, 254
proteus syndrome, 264
RRP, 263
staphylococcal and bacterial, 263
varicose and cystic bronchiectasis, 253
Mycophenolate mofetil (MMF), 430
Myeloperoxidase (MPO), 130, 167

N
NAMIDD. *See* Nonamyloidotic monoclonal immunoglobulin deposition disease (NAMIDD)
Nanoparticle induced ILD, 486–487
Nasal-type T/NK lymphomas, 508, 509
Necrotizing crescentic glomerulonephritis, 141
Negative pressure pulmonary edema (NPPE), 570
Nephrotic syndrome, 98, 99, 105
Neurofibromatosis type 1 (NF1), 533, 603–604
Niemann-Pick disease (NPD), 223–224, 601–602
NK2 Homeobox 1 (NKX2-1) mutations, 605
NLH. *See* Nodular lymphoid hyperplasia (NLH)
Nodular amyloidosis, 592
Nodular lymphoid hyperplasia (NLH), 289, 496, 498
Nonamyloidotic monoclonal immunoglobulin deposition disease (NAMIDD), 93, 592
Non-specific interstitial pneumonia (NSIP)
  alveolar interstitium, 379, 380
  antisynthetase antibody, ILD, 407, 409
  clinical course, 359
  CT patterns, 398, 399
  diagnostic evaluation, 358
  epidemiology, 358
  fibrosis, 382, 383
  ground-glass attenuation, 380, 382, 383
  histopathology, 359–360
  history and definition, 357–358
  lung fibrosis, 402
  OP, 368
  presentation, 358
  pulmonary fibrosis, 395–396
  radiology, 358–359
  treatment, 359–360
Non-tuberculous mycobacteria (NTM), 467–468
NPD. *See* Niemann-Pick disease (NPD)
NPPE. *See* Negative pressure pulmonary edema (NPPE)
NSIP. *See* Non-specific interstitial pneumonia (NSIP)
NTM. *See* Non-tuberculous mycobacteria (NTM)

O
Organizing pneumonia (OP)
  and AE, 469
  AFOP, 374–375, 561
  allogeneic HSCT, 522–523
  BAL (*see* Bronchoalveolar lavage (BAL))
  breast cancer, radiation therapy, 371–372
  buds, granulation tissue, 364, 368
  cancer mimics, 581–582
  cocaine, 170
  COP (*see* Cryptogenic organizing pneumonia (COP))
  corticosteroids (CS), 430
  definition, 363
  diagnostic criteria, 368, 369
  differential diagnosis, 370–371
  diffuse infiltrative form, 368
  disorders, 368, 369
  eosinophilia, 246
  epidemiology, 363–364
  fibroblasts, 364
  ICEP, 230
  imaging patterns, 368
  intraalveolar fibrosis, 364
  isolated nodular, 367
  multifocal alveolar opacities, 365–367
  polymyositis, 407, 408
  proliferative bronchiolitis, 20, 25
  pulmonary capillaritis, 161
  respiratory failure, 373–374
  signs and symptoms, 365
  Sjögren's syndrome, 402
  SOP (*see* Secondary organizing pneumonia (SOP))
  systemic lupus erythematosus (SLE), 396, 397
  transbronchial biopsy, 370
  treatment, 372–373
  UIP, 318
Orphan lung diseases
  clinical trials, 2
  definitions, 1
  diagnostic challenges, 1–2
  drugs, 2
  empowerment of patients, 3
  expert centres, 2
  orphanet, 3
  patient organisations, 2
  rare pulmonary diseases, 1
  research, 3
Orphan tracheopathies
  anatomic considerations, 73
  central airway diseases, 73, 87
  clinical presentation, 73
  CT scan imaging, 87
  etiology, 74
  granulomatosis with polyangiitis, 83–84
  idiopathic subglottic stenosis, 74–76
  relapsing polychondritis, 82–83
  sarcoidosis, 86–87
  systemic diseases, 81
  tracheal diseases, 73
  tracheobronchial amyloidosis, 84–86
  tracheobronchomegaly, 80–81
  tracheobronchopathia osteochondroplastica, 76–78
  tracheomalacia, 78–80
Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT), 143
Oxygen therapy, 281

P
PAA. *See* Pulmonary artery aneurysm (PAA)
PAH. *See* Pulmonary arterial hypertension (PAH)
PAM. *See* Pulmonary alveolar microlithiasis (PAM)
P-ANCA. *See* Perinuclear fluorescence-labeling pattern (P-ANCA)
PAP. *See* Pulmonary alveolar proteinosis (PAP)
Papillomatosis, 263, 591
Parenchymal lung disease, 277, 280, 423, 530
Parenchymal pulmonary amyloidosis, 101–102
PAT. *See* Pulmonary artery thrombosis (PAT)
PCD. *See* Primary ciliary dyskinesia (PCD)
PCH. *See* Pulmonary capillary hemangiomatosis (PCH)
PDGF. *See* Platelet derived growth factor (PDGF)
Perinuclear fluorescence-labeling pattern (P-ANCA), 113, 117, 118, 161, 164, 166, 564
PFTs. *See* Pulmonary function tests (PFTs)
PH. *See* Pulmonary hypertension (PH)
PHD. *See* Primary pulmonary Hodgkin's disease (PHD)
Platelet derived growth factor (PDGF), 120, 178, 240
Plateletderived growth factor receptor-alpha *(PDGFA)* gene, 120
PLCH. *See* Pulmonary Langerhans' cell histiocytosis (PLCH)
Pleural disease, 277

Pneumonic-type lung adenocarcinoma (PTLA), 582–583
Positron-emission tomography (PET), 117, 118, 185
Post-transplantation lymphoproliferative disorders (PTLD), 510, 512
PPL. *See* Primary pulmonary lymphomas (PPL)
Pregnancy and pulmonary AVMs, 194
Preventative transcatheter embolotherapy, 193–194
Primary ciliary dyskinesia (PCD)
  air liquid interface cell culture techniques, 32
  chronic infection, 32
  ciliary dyskinesia and Kartagener syndrome, 32, 35
  embryonic node dysfunction, 32
  genes implication, 34, 36
  genetic testing, 34
  immunofluorescence microscopy analysis, 34
  motile cilia, 32–34
  mutations, 34
  nitric oxide levels, 32
Primary pulmonary Hodgkin's disease (PHD), 508, 510
Primary pulmonary lymphomas (PPL)
  B-cell NHL, 499
  classification, 499
  definition, 499
  diagnosis, 510–511
  follicular lymphoma (FL), 503–504
  high-grade primary large pulmonary B cell lymphomas, 504
  LYG, 506–507
  MALT, 499–501
  PHD, 508, 510
  PTLD, 510
  pulmonary plasmacytoma, 501–503
  staging, 511–512
  T/NK-cell, 507–508
  treatment, 512
Proliferative bronchiolitis, 20, 25
Proteus syndrome, 264
PTLA. *See* Pneumonic-type lung adenocarcinoma (PTLA)
PTLD. *See* Post-transplantation lymphoproliferative disorders (PTLD)
Pulmonary alveolar microlithiasis (PAM)
  differential diagnosis, 310–312
  disease course, 309–310
  epidemiology, 305–306
  etiopathogenesis, 306–308
  features, 305
  pathology, 308
  symptoms and signs, 308–309
Pulmonary alveolar proteinosis (PAP)
  abnormality, surfactant clearance, 285
  autoimmune, 286–289
  cancer, 289–290
  definition, 285
  genetics, 290
  GM-CSF receptor, genetic defect, 291
  immune deficiency, 289
  lysinuric protein intolerance, 291
  monomac syndrome, 291
  SFTPB, SFTPC, ABCA3 and NKX2-1, 290–291
  surfactant homeostasis, 8, 285
  telomerase mutation complex, 292
  toxic particles, inhalation, 290
Pulmonary amyloidosis, 591–592
Pulmonary arterial hypertension (PAH)
  complications, 196
  description, 196
  management of, 196
  right heart failure, 196
  symptoms, 196
Pulmonary artery aneurysm (PAA)
  description, 183–184
  treatment, 185
Pulmonary artery sarcoma, 586–587
Pulmonary artery thrombosis (PAT)
  description, 184
  treatment, 185–186
Pulmonary AVMs
  chest-x-rays, 191–193
  diffuse, 194–195
  HHT (*see* Hereditary hemorrhagic telangiectasia (HHT))
  and pregnancy, 194
Pulmonary capillaritis
  etiologies (*see* Etiology)
  histology, 161
Pulmonary capillary hemangiomatosis (PCH), 172, 529, 535, 536
Pulmonary fibrosis
  acute exacerbation, 341
  treatment of, 342
Pulmonary function tests (PFTs)
  BAL neutrophil levels, 385
  BOS, 520, 521
  chest x-ray, 105
  chronic bronchiolitis, adults, 23
  DIP, 356
  FVC/DLco ratio, 381–382
  HP, 461
  hypoxia, 382
  maximal exercise testing, 382
  NPD-B, 223
  OP, 365
  PLCH, 440–441
  spirometric volumes, 382
  staging severity, 381
Pulmonary hypertension (PH)
  classification, 529–530
  CPFE, 532–533
  definition, 529
  description, 195, 281
  HHT, 534–535
  LAM, 533–534
  liver VMs (*see* Liver VMs)
  neurofibromatosis type 1 (NF1), 533
  PLCH, 531–532
  PVOD/PCH, 535–536
  sarcoidosis, 530–531
Pulmonary Langerhans' cell histiocytosis (PLCH)
  bronchoscopy and BAL, 444
  chest radiography, 441
  clinical features, 438–440
  course and prognosis, 447–448
  description, 436, 592
  diagnosis, 445
  epidemiology, 437
  FDG-PET, 593
  Hand–Schuller–Christian disease, 436
  HRCT, 441–444
  lung biopsy, 444
  multisystem disease, 436
  pathogenesis, 437–438
  pathology, 444–445
  PH, 531–532
  pneumothorax, 593
  pulmonary function tests, 440–441
  single-system disease, 436

smoking exposure, 592
treatment, 445–447
Pulmonary-renal syndrome, 134, 140, 141, 159, 164
Pulmonary veno-occlusive disease (PVOD), 535–536
PVOD. *See* Pulmonary veno-occlusive disease (PVOD)

R
RA. *See* Rheumatoid arthritis (RA)
Radioallergosorbent tests (RASTs), 63
Radio-immunoassay (RIA), 57
Rare diffuse lung diseases
CFTR, 598
clinical and diagnostic aspects, 605, 606
histopathologic and radiographic features, 605, 607
HPS, 597–599
idiopathic interstitial pneumonia, 598
lysosomal lipid storage disease, 600–604
monogenic diseases, 597
pulmonary fibrosis, 597, 598
surfactant dysfunction disorders, 604–605
telomeres, 599–600
Rassmussen's aneurysms, 185
Raynaud's syndrome, 116
RB. *See* Respiratory bronchiolitis (RB)
RB-ILD. *See* Respiratory bronchiolitis interstitial lung disease (RB-ILD)
RDD. *See* Rosai–Dorfman disease (RDD)
Reactive pulmonary lymphoproliferative disease
axillary nodes, 496
CD, 496–498
chest and abdomen, 496
follicular bronchitis/bronchiolitis, 499
intrapulmonary lymph nodes, 493, 499
LIP, 498–499
NLH, 498
Recurrent respiratory papillomatosis (RRP), 263
Relapsing polychondritis, 82–83
Renal angiomyolipoma, 277–278
Respiratory bronchiolitis (RB)
cigarette smokers, 353, 448
description, 20
interstitial lung diseases, 435
Respiratory bronchiolitis interstitial lung disease (RB-ILD)
clinical features, 448–449
description, 448
diagnostic evaluation, 353
epidemiology, 353, 448
histopathology, 354, 355, 449–450
history and definition, 353
presentation, 353
prognosis and therapy, 450–451
radiology, 354, 450
smoking, 436
treatment, 354
Respiratory diseases
systemic AA amyloidosis, 96–98
systemic AL amyloidosis, 98–100
Respiratory tract, 100
Rheumatoid arthritis (RA)
anti-CCP positivity, 422–423
bronchiolitis, 24, 39
classification, 396–398
combined pulmonary fibrosis and emphysema, 400
constrictive bronchiolitis, 25
CPFE syndrome, 329–330
cyclosporine and tacrolimus, 431
drug-induced lung disease, 400–401
exacerbation, 399
GPA, 129
histopathological patterns, 398
interstitial lung disease, 398
methotrexate (MTX), 431
PHD, 508
radiographical patterns, 398–399
rheumatoid nodules, 399–400
rituximab, 144
treatment, 399
Rosai–Dorfman disease (RDD)
description, 222
imaging features, 222–223
immunological abnormalities/autoimmune events, 222
SHML, 222
treatment, 223
RRP. *See* Recurrent respiratory papillomatosis (RRP)

S
Sarcoidosis
in African Americans, 7
central airways, 86–87
differential diagnosis, 21
non-necrotizing granulomas, 86
treatment, 87
Sarcoidosis-associated PH (SAPH), 530–531
Secondary lymphomas, 512–513
Secondary organizing pneumonia (SOP)
causes, 371
and COP, 372, 373
description, 363
Serum amyloid A protein (SAA), 91
SHML. *See* Sinus histiocytosis with massive lymphadenopathy (SHML)
Short tau inversion recovery (STIR), 181
Shrinking lung syndrome, 396, 397
Sinus histiocytosis. *See* Rosai–Dorfman disease (RDD)
Sinus histiocytosis with massive lymphadenopathy (SHML), 222
Sjögren's syndrome (SS)
amyloidosis, 262, 404–405
anti-SS-A (Ro) and SS-B (La) antibodies, 160
classification, 401
CPFE, 330
CTD, 421
cysts, 261, 404
GVHD, 524
histopathology, 402
HRCT, 428, 429
LIP, 403
lung fibrosis, UIP pattern, 402–403
NLH, 591
NSIP, 402
organizing pneumonia, 402
prevalence, ILD, 401
pulmonary amyloidosis associated with, 102
pulmonary lymphoma, 404
sarcoidosis, 405–406
treatment, 403
SLE. *See* Systemic lupus erythematosus (SLE)
SOP. *See* Secondary organizing pneumonia (SOP)
SS. *See* Sjögren's syndrome (SS)
SSc-ILD. *See* Systemic sclerosis-interstitial lung disease (SSc-ILD)
STIR. *See* Short tau inversion recovery (STIR)

Surfactant dysfunction disorders
ABCA3 deficiency, 604–605
NKX2-1/TITF1 mutations, 605
SFTPB deficiency, 604
SFTPC deficiency, 604
Surfactant protein B (SFTPB) deficiency, 604
Surfactant protein C (SFTPC) deficiency, 604
Systemic amyloidosis. *See* Amyloidosis
Systemic diseases
auto-antibody type, 329
CPFE syndrome at chest CT, 329–330
at HRCT, 329
immune response, 330
interstitial pneumonitis, 330
microscopic polyangiitis, 331
Systemic lupus erythematosus (SLE)
acute lupus pneumonitis, 163
ALP, 391–394
ARDS, 395
catastrophic antiphospholipid syndrome, 394, 395
classification, 391, 392
DAH, 394–395
dermatopolymyositis, 411, 412
inflammatory idiopathic myopathy, 411
LIP, 396
lung fibrosis, 395–396
negative prognostic factors, 163
organizing pneumonia has (OP), 396, 397
pneumothorax and pneumomediastinum, 409
shrinking lung syndrome, 396, 397
thrombocytopenia with DAH, 159
treatment, 163
UCTD, 423
Systemic sclerosis-interstitial lung disease (SSc-ILD)
cellular NSIP, 379, 380
corticosteroid, 386
cyclophosphamide, 385–386
description, 379
evolution, dyspnoea, 381
finger clubbing, 381
gas-transfer and gas exchange, 386–388
genetic associations, 380–381
HRCT (*see* High-resolution computed tomography (HRCT))
mild/extensive severity staging system, 384, 387
PFTs, 381–382
prevalence, 379
prognostic evaluation, 383–385
respiratory symptoms, 381
risk factors, 380
rituximab, 386

T
Takayasu arteritis (TA)
adults, 177
chronic large-vessel granulomatous vasculitis, 177
clinical features, 178–180
epidemiology, 177
imaging studies, 180–181
laboratory findings, 180
pathologic features, 177–178
prognosis, 182
therapeutic management, 181–182
TBB. *See* Transbronchial lung biopsy (TBB)
TBLB. *See* Transbronchial lung biopsy (TBLB)
Telomerase-associated pulmonary fibrosis, 599–600
Thymus and activation-regulated chemokine (TARC), 56, 62, 240, 244
Thyroid transcription factor 1 (TITF1) mutations, 605
Tracheobronchial amyloidosis, 84–86, 101
Tracheobronchomegaly, 39, 74, 80–81
Tracheobronchopathia osteochondroplastica, 76–78
Tracheomalacia, 78–80, 83
TRALI. *See* Transfusion-related acute lung injury (TRALI)
Transbronchial lung biopsy (TBB), 369, 370
Transbronchial lung biopsy (TBLB), 319
Transfusion-related acute lung injury (TRALI), 557–558
Treatment
ABPA
antifungal drugs, 65–66
bronchial colonisation, 64
exacerbations, 64
fiberoptic bronchoscopy, 66
goals, 64
inhaled corticosteroids, 66
long-term prognosis, 64
molecules, 64
monitoring, 64
nebulised amphotericin, 66
omalizumab, 66
oral corticosteroids, 64–65
CSS, 121–122
diffuse bronchiectasis
airway clearance technique, 43–44
antibiotic therapies, 43
anti-inflammatory management, 44–45
gene therapy, 45–46
immune therapy, 45
infections management, 44
surgery, 45
GPA
adverse effects, 147
anti-TNF-α, 146
corticosteroids, 143
cotrimoxazole, 146
cyclophosphamide, 143–144
intensive chemotherapy, 147–148
intravenous immunoglobulins, 146
localized/limited/early systemic GPA, 145–146
maintenance therapy, 144–145
manifestations, 147
open-label study, 148
patient, 143
phases, 143
plasma exchange, 146
relapsing and refractory, 147
rituximab, 144
PLCH, 445–447
Tropical eosinophilia, 241–242
Tuberous sclerosis, 279–280

U
UIP. *See* Usual interstitial pneumonia (UIP) pattern
Unclassifiable interstitial pneumonia, 361
Undifferentiated CTD (UCTD)
autoimmune-featured ILD, 425
idiopathic pulmonary fibrosis (IPF), 426
interdisciplinary divide, 426–427
lung-dominant CTD, 426
proposed criteria, 423–425

United Network for Organ Sharing (UNOS) policy, 207–208
US Orphan Drug Act, 5
Usual interstitial pneumonia (UIP) pattern
  HRCT scan, 315–316
  idiopathic and non-idiopathic interstitial, 319–320
  in IPF, 319
  lung biopsy, 317–319
  serologic testing, CTD, 320
  subpleural basal reticular abnormalities, 321
  on surgical lung biopsy, 321, 322

V
Valvular heart disease, 168, 552
Vascular endothelial growth factor (VEGF), 178, 196, 276
Vascular malformations (VMs). *See* Liver VMs
VEGF. *See* Vascular endothelial growth factor (VEGF)
Venous/arterial thrombosis, 182

W
Wegener's granulomatosis, 116, 118–120. *See also* Granulomatosis with polyangiitis (GPA)
Williams–Campbell syndrome, 39, 78

X
X-linked agammaglobuinemia (XLA), 37–38

Y
Young's syndrome, 34–35