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18.11

Diffuse parenchymal lung diseases

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18.11.1 Diffuse parenchymal lung disease: An introduction

F. Teo and A.U. Wells

ESSENTIALS

The nomenclature of diffuse parenchymal lung disease (also known as interstitial lung disease) has caused a great deal of confusion, with use of complicated histopathological terms not always corresponding to clinico-radiological entities. Five major groupings are now recognized: (1) idiopathic interstitial pneumonias; (2) diseases associated with systemic conditions, including rheumatological disorders; (3) diseases caused by environmental triggers or drugs; (4) granulomatous diseases; and (5) other diffuse lung diseases.

Idiopathic interstitial pneumonias

Classification is based on recognition of clinical, radiological, and histopathological patterns, as opposed to the purely histopathological terminology. Diagnosis is complicated by the large number of disorders grouped within the diffuse parenchymal lung diseases. A systematic diagnostic algorithm, based upon careful clinical evaluation and a logical sequence of tests, is essential. Clinical history, clinical examination, chest radiography, pulmonary function tests, and selective blood tests should be followed by high-resolution CT, bronchoalveolar lavage (in some cases), and lung biopsy (in a few cases).

The chronic diffuse parenchymal lung diseases can be broadly subclassified into five patterns of longitudinal disease behaviour, based upon cause, severity, the relative degree of inflammation and fibrosis, and observed change in the short term. Each clinical pattern is associated with a separate approach to management.

Reversible and self-limited disease—usually caused by an extrinsic agent and typically responds to withdrawal of an offending agent.

Reversible major disease with risk of progression, with or without supervening fibrosis—a feature of drug-induced lung disease and some other conditions; usually treated with high-dose corticosteroids, with dose reduction to minimum possible once inflammation is controlled.

Residual but stable fibrotic disease—most commonly encountered in sarcoidosis, following drug-induced lung disease, and in patients with formerly active rheumatological disorders; treatment is not required.

Progressive fibrotic disease—in which stabilization is a realistic goal—frequently seen in sarcoidosis, hypersensitivity pneumonitis, rheumatological conditions, and in many patients with fibrotic nonspecific interstitial pneumonia; aggressive initial treatment is usually warranted and long-term therapy is often required.

Inexorably progressive fibrotic disease—the hallmark of idiopathic pulmonary fibrosis; long-term treatment may slow disease progression and reduce mortality; early recognition of relentless progression is important when lung transplantation is possible, and to assure provision of effective palliation when it is not.

Definition

The nomenclature of diffuse parenchymal lung disease has caused confusion over the decades. Contributory factors include nonstandardized terminology (e.g. 'extrinsic allergic alveolitis' and 'hypersensitivity pneumonitis' as alternative terms for the same entity), the inappropriate grouping of otherwise diverse clinicopathological entities (previous use of the umbrella term 'cryptogenic fibrosing alveolitis/idiopathic pulmonary fibrosis' to describe all idiopathic interstitial pneumonias), and the use of similarly

worded yet distinct disease definitions (e.g. bronchiolitis obliterans organizing pneumonia and bronchiolitis obliterans syndrome). The terminology has been refined as our understanding of disease mechanisms, presentations, and prognosis has evolved.

Diffuse parenchymal lung disease is synonymous with interstitial lung disease. The former terminology reflects, perhaps more aptly, the fact that disease processes involve the lung parenchyma, but also the airspace components of the acini in many cases. Infective pneumonias, pulmonary oedema, and some malignancies involve the acinar regions of the lung but are not, by convention, grouped with the diffuse parenchymal lung diseases, although they may present with similar clinical and radiological findings and should be considered in the formulation of a differential diagnosis. However, a decision was made to adopt the term interstitial lung disease in the British Thoracic Society (in collaboration with the Thoracic Society of Australia and New Zealand and Irish Thoracic Society) document to achieve consistency with other international guidelines.

Specific disease will be considered in subsequent chapters. In this introduction, a broad approach to the classification of the diffuse lung diseases and their diagnosis and investigation will be discussed.

Classification

Diffuse parenchymal lung diseases can be subdivided into five major groupings:

1. Idiopathic interstitial pneumonias
2. Systemic disease (including rheumatological) associated interstitial lung disease
3. Environmental or drug related interstitial lung disease
4. Granulomatous diseases
5. Other diffuse lung diseases (e.g. histiocytosis and lymphangioleiomyomatosis)

In most patients with environmentally and drug-induced lung disease, granulomatous lung disease or systemic disease-associated interstitial lung disease (groups 2–5), the cause and, thus, the diagnosis is immediately apparent or is rapidly disclosed by standard investigations detailed next. By contrast, diagnosis is less straightforward when a cause is not immediately apparent (group 1). By definition, most of these patients can be categorized as having one of the idiopathic interstitial pneumonias, discussed in detail in the remainder of this chapter. Table 18.11.1.1 lists diseases of known and unknown cause within the broad headings given here, and disorders that present more acutely are shown in Table 18.11.1.2.

Idiopathic interstitial pneumonias

The diseases grouped as the 'idiopathic interstitial pneumonias' have given rise to particular confusion, largely because terms used to describe histopathological patterns have been used interchangeably but inaccurately with disease 'labels'. In 1944, Hamman and Rich first described a presentation of rapidly

Table 18.11.1.1 Diffuse parenchymal lung disease

Associated with systemic diseases
Rheumatological: Systemic sclerosis, rheumatoid arthritis, polymyositis/dermatomyositis, systemic lupus erythematosus, Sjögren's syndrome, ankylosing spondylitis
Vasculitis: Wegener's granulomatosis, Churg– Strauss granulomatosis, microscopic polyangiitis, pulmonary–renal syndrome (including Goodpasture's syndrome), capillaritis, Behçet's syndrome
Vascular: Primary pulmonary hypertension, idiopathic pulmonary haemosiderosis, pulmonary veno-occlusive disease, antiphospholipid syndrome
Diseases caused by environmental triggers or drug ingestion
Hypersensitivity pneumonitis: fungal, bacterial, avian, chemical Fibrogenic inorganic dusts: asbestosis, silica, hard metal alloyberyllium, coal, aluminium Therapeutic agents,[a] illicit drugs, radiation, pesticides, oxygen and other inhaled gases
Granulomatous diseases
Sarcoidosis, hypersensitivity pneumonitis, berylliosis, Langerhans cell histiocytosis, Wegener's granulomatosis, Churg–Strauss syndrome, lymphomatoid granulomatosis, bronchocentric granulomatosis
Idiopathic interstitial pneumonias
Idiopathic pulmonary fibrosis, nonspecific interstitial pneumonia, desquamative interstitial pneumonia, respiratory bronchiolitis–interstitial lung disease, acute interstitial pneumonia, cryptogenic organizing pneumonia, lymphocytic interstitial pneumonia, idiopathic pleuroparenchymal fibroelastosis
Other diffuse lung diseases
Inherited disorders: tuberous sclerosis, neurofibromatosis, Hermansky–Pudlak syndrome, lipid storage disorders, familial idiopathic pulmonary fibrosis
Pulmonary eosinophilia: known causes (fungi, parasites, drugs), acute idiopathic, chronic idiopathic
Lymphangioleiomyomatosis
Alveolar proteinosis
Alveolar microlithiasis
Amyloidosis
Chronic aspiration

[a] see www.pneumotox.com for full listing.

Table 18.11.1.2 Acute presentations of diffuse parenchymal lung disease: differential diagnosis

Primary diffuse parenchymal lung disorders
Acute interstitial pneumonia
Acute exacerbations of idiopathic pulmonary fibrosis
Diffuse alveolar haemorrhage due to vasculitis or coagulopathy
Fulminant cryptogenic and secondary organizing pneumonia
Acute pneumonitis due to rheumatological disease
Hypersensitivity pneumonitis
Acute pulmonary eosinophilia
Drug-induced lung disease
Mimics of diffuse parenchymal lung disease
Pulmonary oedema due to left ventricular failure, uraemia or other causes
Infection, especially opportunistic with *Pneumocystis carinii*
Extensive, rapidly progressive metastatic malignancy

Table 18.11.1.3 American Thoracic Society/European Respiratory Society nomenclature of idiopathic interstitial pneumonias

Clinical-radiological diagnosis	Pathology pattern
Cryptogenic fibrosing alveolitis (idiopathic pulmonary fibrosis)	Usual interstitial pneumonia
Nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia (provisional)
Desquamative interstitial pneumonia (alternative name: alveolar macrophage pneumonia)	Desquamative interstitial Pneumonia
Respiratory bronchiolitis–interstitial lung Disease	Respiratory bronchiolitis–interstitial lung disease
Acute interstitial pneumonia	Diffuse alveolar damage
Cryptogenic organizing pneumonia	Organizing pneumonia
Lymphocytic interstitial pneumonia	Lymphocytic interstitial pneumonia
Pleuroparenchymal fibroelastosis	Pleuroparenchymal fibroelastosis

progressive fatal disease, in which the cardinal histological features were interstitial inflammation and fibrosis. It subsequently became clear that chronic insidiously progressive fibrosing disease was not uncommon. A typical clinical picture was defined, consisting of progressive dyspnoea, bilateral predominantly basal crackles on auscultation, reticulonodular predominantly basal abnormalities on chest radiography, and a restrictive ventilatory defect on lung function testing. This clinical entity was termed 'cryptogenic fibrosing alveolitis (CFA)' or 'idiopathic pulmonary fibrosis (IPF)'. However, it became clear that the outcome associated with this presentation, hereafter termed the 'CFA clinical syndrome', was highly heterogeneous. Although most patients progressed inexorably to a fatal outcome, usually within three to four years, a more insidious course was seen in a significant minority, and in 10–15% of cases there was a response to corticosteroid therapy and, usually, a good long-term outcome.

Histological patterns of disease encountered in the CFA clinical syndrome were first classified by Liebow in 1975 as usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), bronchiolitis obliterans with usual interstitial pneumonia (BIP), lymphocytic interstitial pneumonia (LIP), and giant cell interstitial pneumonia. However, it subsequently became clear that these patterns of disease were also present outside an idiopathic setting. The most frequent, UIP, was occasionally found in connective tissue disease, drug-induced lung disease, and chronic hypersensitivity pneumonitis, and LIP was most commonly associated with rheumatological disease and, more recently, AIDS-related disease. Giant cell interstitial pneumonia was seldom idiopathic but was caused by exposure to hard metals (cobalt, tungsten carbide, titanium salts). It also became apparent that the historical histological pattern of UIP did, in fact, encompass separate patterns of UIP and nonspecific interstitial pneumonia (NSIP), which denoted a better outcome.

These considerations led to a revision of Liebow's classification. The interstitial pneumonias of known cause were removed (although smoking-related disorders were retained). The revised classification, in an attempt by a nomenclature committee of the American Thoracic Society and European Respiratory Society in 2001 to integrate clinical, radiological, and histopathological patterns as opposed to hitherto purely histopathological terminology, included UIP, NSIP, DIP, respiratory bronchiolitis–interstitial lung disease (RB-ILD), diffuse alveolar damage (DAD), LIP, and cryptogenic organizing pneumonia (Table 18.11.1.3). The term CFA became synonymous with IPF, requiring an underlying histological pattern of UIP or compatible high-resolution computed tomography (HRCT) appearances, and was distinguished from the nonspecific 'CFA clinical syndrome'. It was also recognized that different histological patterns may be found within the same disease (e.g. NSIP with UIP pattern in idiopathic pulmonary fibrosis), and this underscored the importance of integrating clinical, radiological, and pathological information in arriving at a unifying diagnosis.

In 2013, the American Thoracic Society and European Respiratory Society further revised the classification of idiopathic interstitial pneumonias (IIP). NSIP, hitherto a provisional diagnosis with poorly characterized clinical and radiologic features, became accepted as a distinct major clinical entity, and idiopathic LIP was classified as a rare IIP. Major IIPs were distinguished from rare (idiopathic LIP and pleuroparenchymal fibroelastosis) and unclassifiable IIPs, and subgrouped into chronic fibrosing (IPF and NSIP), smoking-related (RB-ILD and DIP) and acute/subacute IIPs (acute interstitial pneumonia and cryptogenic organizing pneumonia). (Table 18.11.1.3). Rare histological patterns of acute fibrinous and organizing pneumonia and interstitial pneumonias with a bronchiolocentric distribution were introduced. Finally, a clinical disease behaviour classification was proposed to capture thought processes of clinicians and serve as a rationale for treatment and monitoring decisions in disease that is difficult to classify.

The pattern of UIP and its associated disorder, IPF, and cryptogenic organizing pneumonia are covered separately in Chapter 18.11.2. The other idiopathic interstitial pneumonias are reviewed briefly next.

Major idiopathic interstitial pneumonias

Chronic fibrosing interstitial pneumonias

Idiopathic pulmonary fibrosis

See Chapter 18.11.2.

Nonspecific interstitial pneumonia

Nonspecific interstitial pneumonia is the least satisfactory entity among the idiopathic interstitial pneumonias. Histologically, there is variable interstitial inflammation and fibrosis but, unlike usual interstitial pneumonia, the pattern with which it is most likely to be confused, disease is uniform throughout biopsy specimens, both in severity and in the age of fibrosis (Fig. 18.11.1.1). Fibroblastic foci, the cardinal finding in usual interstitial pneumonia, are absent or sparse. The radiological and clinical manifestations of NSIP are diverse. Inflammation predominates in a few cases and the treated outcome is uniformly good, but in most patients with fibrotic NSIP, fibrosis is as prominent as, or more prominent than, inflammation.

Certain clinico-radiological profiles are increasingly recognized in NSIP:

1. NSIP/IPF: the most prevalent profile in most European countries and the United States, it is clinically and physiologically indistinguishable from that of IPF, despite major outcome differences. On HRCT, the basal distribution of disease is similar to that of IPF, but unlike IPF, there is prominent ground-glass attenuation and honeycombing is absent or minimal (Fig. 18.11.1.2).
2. NSIP/OP: this profile is typically present in pulmonary fibrosis associated with inflammatory myopathy. In this large subgroup, predominating in reports from South Korea and Japan, the clinical and radiological features are those of organizing pneumonia admixed with fibrosis and there is a prominent lymphocytosis on bronchoalveolar lavage.

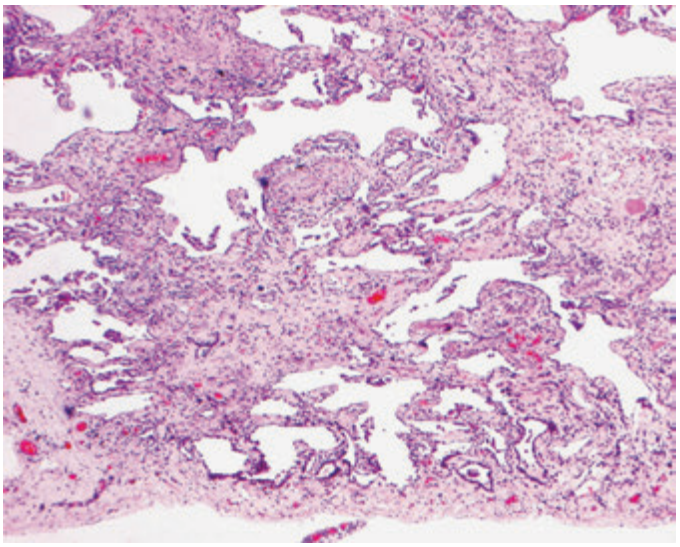

Fig. 18.11.1.1 A case of fibrotic nonspecific interstitial pneumonia showing established interstitial fibrosis with a moderate degree of associated chronic inflammation. In areas of affected lung, the features appear homogeneous and diffuse, unlike appearances in usual interstitial pneumonia (see Chapter 18.11.2), and fibroblastic foci are not present.

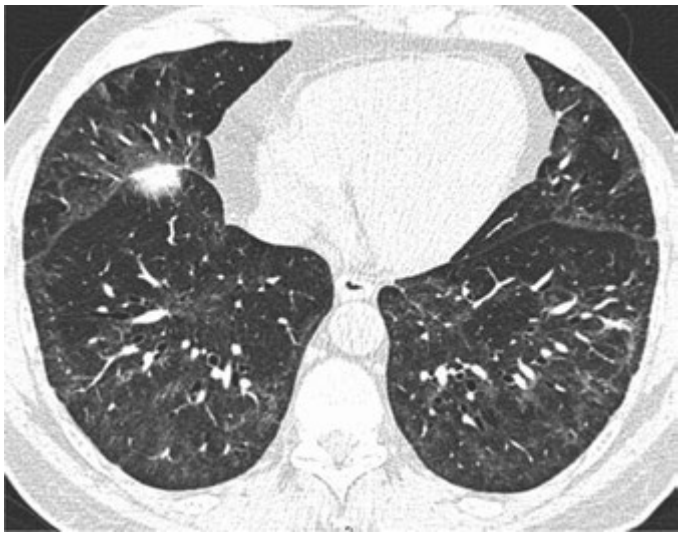

Fig. 18.11.1.2 HRCT appearances from the lower lung zone in a patient with biopsy-proven fibrotic NSIP. There is widespread ground-glass attenuation with mild traction bronchiectasis and, in some regions, a subtle admixed reticular element, resulting in a sense of increased texture within abnormal lung.

3. NSIP/HP: this profile arose mainly from reports in France and Mexico, with clinical exposure histories, HRCT and bronchoalveolar lavage (BAL) features closely resembling that of hypersensitivity pneumonitis, despite the absence of granulomas in biopsy tissue. In more recent reports, a subgroup of hypersensitivity pneumonitis patients with typical NSIP at biopsy is recognized.

The prognosis is variable. Corticosteroid and immunosuppressive therapy are often effective in producing regression or stabilization of disease, but in a few cases, largely confined to those presenting with clinical and HRCT features overlapping with those of IPF, there is inexorable progression to a fatal outcome despite treatment.

Smoking-related interstitial pneumonias

Desquamative interstitial pneumonia

The cardinal histological feature is diffuse accumulation of macrophages in alveolar spaces in a uniform pattern, variably associated with minor interstitial inflammation and fibrosis (Fig. 18.11.1.3). DIP is a rare disorder almost exclusively found in smokers in their fourth or fifth decades, with a male to female predominance of 2:1. Typical HRCT appearances comprise extensive ground-glass attenuation (Fig. 18.11.1.4). The disease presents with the features of the CFA clinical syndrome, with finger clubbing present in 50% of patients. Unlike IPF, a response to corticosteroids is seen in at least 70% and the longer-term treated outcome in these patients is often good. Current smokers should be advised to quit.

Respiratory bronchiolitis–interstitial lung disease (RB-ILD)

As in DIP, the histological features of RB-ILD are dominated by the presence of pigmented macrophages, but unlike DIP, these accumulate around the bronchioles (respiratory bronchiolitis; see Fig. 18.11.1.5), often with associated peribronchiolar interstitial inflammation and fibrosis, with preserved pulmonary

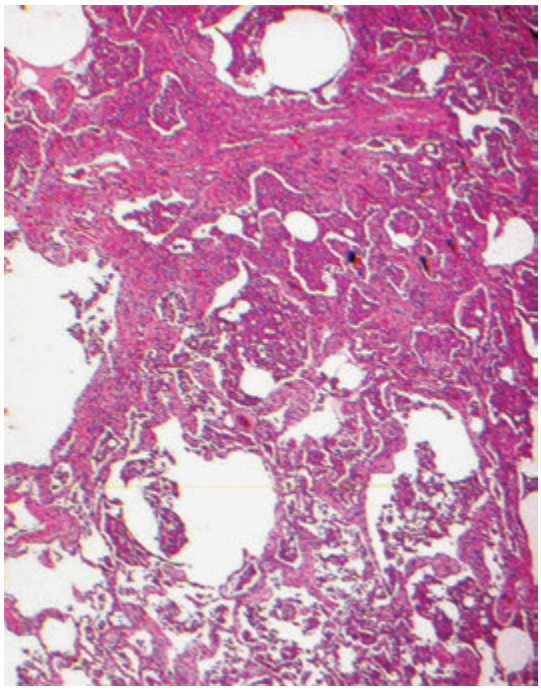

Fig. 18.11.1.3 A case of DIP with typical appearances of macrophage filling of alveolar spaces diffusely within pulmonary acini. There is also mild interstitial fibrosis and focal background emphysema, in keeping with the association between DIP and cigarette smoking.

parenchyma. Typical HRCT findings include bronchial wall thickening, poorly defined centrilobular nodules, and patchy ground-glass attenuation and emphysema. RB-ILD is found only in current or recent former smokers and in many patients, there is overlap

Fig. 18.11.1.4 HRCT appearances in a patient with histologically proven DIP. There is extensive ground-glass attenuation with no traction bronchiectasis or admixed reticular abnormalities. Although typical of DIP, these appearances are nonspecific, denoting a high likelihood of reversible inflammatory disease.

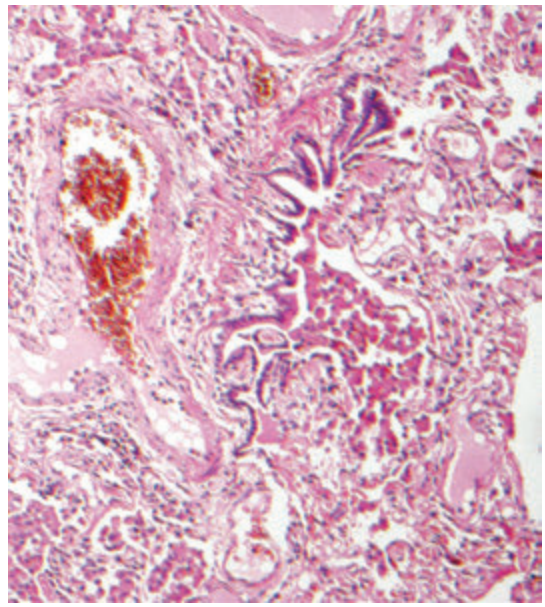

Fig. 18.11.1.5 Biopsy from a patient with respiratory bronchiolitis–associated interstitial lung disease showing macrophages with similar histological appearances to those of DIP, but the aggregation is centred on bronchioles where there is also a mild chronic inflammatory cell infiltrate within the airway walls.

in histological features between RB-ILD and DIP. The histological appearances in RB-ILD are identical to those of asymptomatic respiratory bronchiolitis, which is always present in current smokers. The distinction between RB-ILD and respiratory bronchiolitis is based upon disease severity, as defined by symptoms, the severity of lung function impairment and the extent of disease on HRCT. RB-ILD is diagnosed when a clinically significant diffuse lung disease is considered to be present. It is increasingly recognized that RB-ILD may be diagnosed without surgical lung biopsy in smokers with the aforementioned HRCT features and a macrophage-predominance in bronchoalveolar lavage. The disorder usually has a good outcome and often regresses with smoking cessation but based on limited data, corticosteroid therapy is seldom efficacious.

Acute/subacute interstitial pneumonias

Acute interstitial pneumonia

Acute interstitial pneumonia, also known as the Hamman-Rich syndrome (or idiopathic adult respiratory distress syndrome), is characterized by a histological pattern of diffuse alveolar damage, with hyaline membranes lining damaged alveoli (Fig. 18.11.1.6) and buds of organization in the alveoli of those acini that have been damaged and are undergoing the healing process. Presentation is most commonly reported in the fifth or sixth decade, with no gender predilection. Symptoms are typically heralded by a viral prodrome, with progressive dyspnoea over days to weeks. There is widespread ground-glass consolidation, often with traction bronchiectasis, and dependent consolidation on HRCT. Outcome is fatal in 80–90% of cases. Although high dose corticosteroid therapy and immunosuppressive agents are commonly given, there is no evidence that treatment influences outcome in most cases.

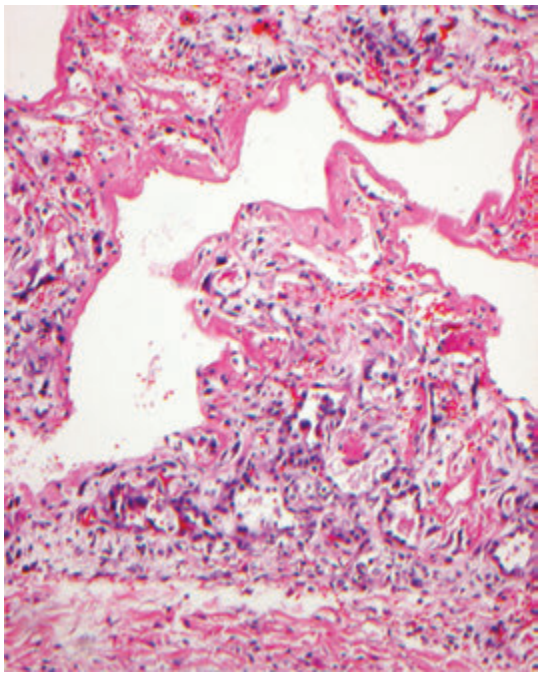

Fig. 18.11.1.6 A case of acute interstitial pneumonia (AIP) showing the exudative phase of diffuse alveolar damage with hyaline membranes lining alveolar walls, indicating AIP when present in an idiopathic setting.

Cryptogenic organizing pneumonia

See Chapter 18.11.3.

Rare idiopathic interstitial pneumonias

Lymphocytic interstitial pneumonia

The histopathological pattern of lymphocytic interstitial pneumonia is most commonly found in patients with rheumatological disease and in immunodeficiency syndromes but can rarely occur as an idiopathic disorder. The histological findings consist of diffuse interstitial lymphocytic infiltration (Fig. 18.11.1.7), variably associated with follicular bronchiolitis. The HRCT features consist of patchy and sometimes extensive ground-glass attenuation with a variable nodular component. Corticosteroid and immunosuppressive therapy is effective in over 50% of cases.

Pleuroparenchymal fibroelastosis

Idiopathic pleuroparenchymal fibroelastosis is a rare condition characterized by histologic evidence of dense intra-alveolar fibrosis and corresponding prominent alveolar wall elastosis with fibrous thickening of the involved visceral pleura. Clinical presentation is often in the fourth or fifth decade of life, with no gender predilection. Radiographic hallmarks are pleural and adjacent parenchymal fibrosis in a predominant upper lobe distribution. Symptoms include cough and shortness of breath evolving over 6 months to years, with a significant number of patients having experienced recurrent infections and recurrent pneumothoraces. Disease progression occurs in 60% of patients with death from disease in 40% in initial reports, although these series are dominated by severe disease and are unlikely to be representative of the whole spectrum of pleuroparenchymal fibroelastosis. There is presently no effective treatment available.

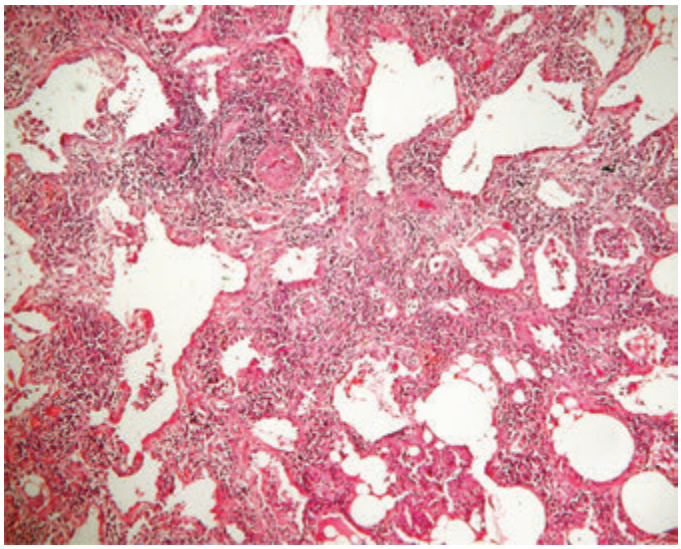

Fig. 18.11.1.7 A case of lymphoid interstitial pneumonia showing dense interstitial chronic inflammation diffusely involving the alveolar parenchyma, in this case associated with minimal interstitial fibrosis.

Diagnostic approach

Diagnosis is complicated by the large number of disorders grouped within the diffuse parenchymal lung diseases. A systematic diagnostic algorithm, based upon careful clinical evaluation and a logical sequence of tests, is essential. This approach can be broken down into in two phases:

Phase 1

1. clinical history
2. clinical examination
3. chest radiography
4. pulmonary function tests
5. selective blood tests

Phase 2

1. high-resolution computed tomography
2. bronchoalveolar lavage
3. lung biopsy

Phase 1

Clinical history

In most patients, the presentation is insidious dyspnoea, variably accompanied by cough which is usually nonproductive. The duration of dyspnoea is diagnostically important: an acute presentation narrows the differential diagnosis considerably (see Table 18.11.1.2).

Wheeze is a useful discriminatory symptom as the presence of an airway-centred component informs the differential diagnosis. Disorders with variable but sometimes prominent wheeze include hypersensitivity pneumonitis, sarcoidosis,

lymphangioleiomyomatosis, and Langerhans cell histiocytosis. Other less frequent respiratory symptoms are also diagnostically useful. Pleuritic chest discomfort often occurs in the rheumatological diseases and occasionally in drug-induced disease, but never in idiopathic pulmonary fibrosis or hypersensitivity pneumonitis. Haemoptysis may be indicative of diffuse alveolar haemorrhage due to capillaritis, occurring in certain disorders: haemoptysis may be trivial, even when haemorrhage is severe. A history of pneumothorax should prompt suspicion of cystic lung disease, especially Langerhans cell histiocytosis and lymphangioleiomyomatosis.

The previous medical history may provide crucial information, including diagnoses of rheumatological disease or other relevant systemic diseases (including vasculitis). Even when no previous systemic diagnosis has been made, the nature of preceding systemic symptoms may point strongly to a hitherto undiagnosed rheumatological disorder. Knowledge of underlying cardiac and malignant disease is also essential as disseminated malignancy and cardiac failure may both simulate diffuse parenchymal lung disease, clinically and radiologically. A detailed list of medications serves to alert the clinician to the possibility of drug-induced lung disease. The agents most frequently responsible include nitrofurantoin, methotrexate, and bleomycin but a long list of other drugs occasionally cause lung disease. The comprehensive website, *pneumotox.com*, provides a rapid and fruitful means of checking possible pulmonary toxicities.

The occupational history should include all occupations from school-leaving: diseases caused by some exposures (including asbestos exposure) manifest decades later. Environmental conditions in which pneumoconiosis most commonly arise include sawing, grinding, and drilling. Hypersensitivity pneumonitis arises from the inhalation of organic dusts including fungal contaminates of hay (as in farmers lung) and avian proteins found on the bloom and in the excreta of domestic birds. Many other organic antigens can give rise to hypersensitivity pneumonitis, with over 200 causes now recognized.

Other relevant historical information includes foreign travel, which may raise the possibility of parasitic infection as an explanation of pulmonary eosinophilia. A history of cigarette smoking identifies a predisposition to Langerhans cell histiocytosis, DIP, and RB-ILD and is also a risk factor for exacerbations of pulmonary vasculitis. Paradoxically, smoking appears to protect against the development of sarcoidosis and hypersensitivity pneumonitis.

Clinical examination

Digital clubbing is common in IPF and NSIP, and is not infrequent in hypersensitivity pneumonitis, but is unusual in the other diffuse parenchymal lung diseases. Predominantly basal fine end inspiratory crackles are a cardinal feature of the CFA clinical syndrome and are expected in IPF and variably present in the other idiopathic interstitial pneumonias. Sporadic crackles are heard in many diffuse parenchymal lung diseases, but are seldom present in sarcoidosis. Expiratory wheeze is indicative of airway disease. Inspiratory squawks are strongly predictive of hypersensitivity pneumonitis or obliterative bronchiolitis. In advanced disease, clinical evidence of secondary pulmonary hypertension should be sought, as oxygen supplementation may have a pivotal role in management.

Relevant systemic findings include ocular disease (in sarcoidosis or vasculitis), skin disease (in sarcoidosis or rheumatological disease), musculoskeletal signs (in rheumatological disease) and neurological abnormalities (mononeuritis multiplex in sarcoidosis, rheumatological disease, and vasculitis; a wide variety of central and peripheral signs in sarcoidosis).

Chest radiography

Chest radiography was formerly a central part of the evaluation of diagnosis of diffuse parenchymal lung disease. Although HRCT has now supplanted chest radiography in routine diagnosis, the chest radiograph continues to provide useful information.

Radiographic findings suggestive of pulmonary fibrosis are a required feature of the CFA clinical syndrome. Patients with fibrosing lung diseases tend have reduced lung volumes. If other clinical features are indicative of IPF, normal-sized or large lungs on chest radiography are suggestive of the coexistence of emphysema and pulmonary fibrosis, a frequent association in cigarette smokers with IPF. Large or normal sized lungs on chest radiography, in association with nodular or reticular shadowing, also occur in Langerhans cell histiocytosis, lymphangioleiomyomatosis (a disorder involving smooth muscle proliferation arising in premenopausal women), and the closely related disorder, tuberous sclerosis. Idiopathic bronchiectasis or cystic fibrosis, with increased radiographic volumes due to hyperinflation, can also be mistaken radiologically for diffuse parenchymal lung disease, although the clinical profile of chronic purulent sputum production is usually discriminatory.

The distribution of disease is often helpful. Primary fibrosing disorders, including IPF, fibrotic NSIP, pulmonary fibrosis in rheumatologic disease and asbestosis, produce predominantly basal reticular or reticulonodular abnormalities, which may also be overtly peripheral when disease is not advanced. By contrast, granulomatous disorders, including sarcoidosis and hypersensitivity pneumonitis (as well as tuberculosis and allergic bronchopulmonary asbestosis) most often have a predominantly upper and mid zone distribution. In the correct clinical setting, chest radiographic findings typical of sarcoidosis (predominantly upper zone fibrotic change, variably associated with lymphadenopathy and hilar retraction towards the apices) often suffice for a confident diagnosis.

The size and shape of abnormalities is sometimes diagnostically useful, although this aspect of radiological evaluation has largely been supplanted by HRCT. Chest radiographic nodules of more than 5 mm in diameter are often present in Wegener's granulomatosis, lymphoma, and other malignancies. Cavitating nodules are a frequent feature in Wegener's granulomatosis, but necrotizing carcinomas and multiple staphylococcal abscesses should also be considered. The presence of nodules of differing size and shape is strongly suggestive of metastatic malignancy. An alveolar filling pattern, consisting of widespread confluent shadowing, usually denotes the presence of life-threatening disease. The differential diagnosis includes pulmonary oedema (due to left ventricular failure or mitral stenosis), diffuse alveolar haemorrhage, uraemia, drug-induced lung disease (and other forms of diffuse alveolar damage), infection (especially opportunistic infection in immunosuppressed patients) and alveolar proteinosis. When widespread confluent shadowing is chronic, alveolar cell carcinoma, lymphoma, and pulmonary eosinophilia should also be considered.

Previous chest radiographs are often highly revealing, especially in the patient presenting with multifocal consolidation. Waxing and waning of consolidation effectively excludes malignant disease and is strongly suggestive of immunologically mediated disorders, including cryptogenic organizing pneumonia, vasculitis, and pulmonary eosinophilia. Fixed consolidation may also occur in all of these disorders but should also prompt suspicion of lymphoma, alveolar cell carcinoma, and chronic infection.

Pleural thickening, with or without effusion, occurs commonly in rheumatological disease, rheumatoid arthritis, and systemic lupus erythematosus. Pleural abnormalities also occur commonly in asbestosis and in Churg–Strauss granulomatosis and Wegener's granulomatosis. The presence of pleural disease should always prompt consideration of a second disease process, including malignancy, heart failure, tuberculosis, pulmonary embolism, and drug-induced lung disease. Pleural involvement is not a feature of uncomplicated hypersensitivity pneumonitis or IPF and is seldom present in the other idiopathic interstitial pneumonias, although occasionally encountered in sarcoidosis and cryptogenic organizing pneumonia.

Symmetrical hilar lymphadenopathy is usually indicative of sarcoidosis, but tuberculosis, lymphoma, and other malignancies should always be considered, especially if the changes are unilateral. Lymphadenopathy is seldom present on chest radiography in other diffuse lung diseases, with the exception of silicosis. Hilar calcification occurs in sarcoidosis, silicosis, and tuberculosis.

Pulmonary function testing

In most patients with diffuse parenchymal lung disease, there is a restrictive ventilatory defect with reduced gas transfer (DL_{CO}). Arterial oxygen tensions (Pao_2) are normal or mildly reduced until disease is advanced, although the alveolar–arterial oxygen gradient is often widened in associated with $Paco_2$ levels that are at the lower end of the normal range. In early disease, maximal exercise testing may unmask abnormalities or, when normal, may reassure the clinician that the disease is not clinically significant. In IPF, maximal exercise testing typically a fall in the Pao_2 and widening of the alveolar–arterial oxygen gradient (A–a gradient), reflecting ventilation–perfusion mismatch and, at maximal exercise, impairment of diffusion. The anatomical dead space to tidal volume ratio (V_D/V_T) normally falls on exercise in the healthy individual but is unchanged or increases in restrictive lung disease. Striking rises in the V_D/V_T ratio are strongly suggestive of disproportionate pulmonary vascular limitation.

A mixed (restrictive-obstructive) ventilatory defect is seen in disorders in which airway involvement is associated with diffuse parenchymal lung disease. This ventilatory pattern most commonly occurs in hypersensitivity pneumonitis, sarcoidosis, and rheumatological disorders. The coexistence of pulmonary fibrosis and emphysema, usually found in cigarette smokers with IPF or fibrotic NSIP, may also give rise to a mixed ventilatory defect, but more commonly, there is spurious preservation of lung volumes and a disproportionate reduction in DL_{CO}.

Blood tests

Routine haematology and biochemical tests have little discriminatory value in the diffuse lung diseases. A peripheral blood eosinophilia (above 1.5 × 109/litre) is a prerequisite for diagnosis of Churg–Strauss vasculitis and may also be indicative of pulmonary eosinophilia (although not always present in that disorder). Increased levels of angiotensin converting enzymes are a helpful ancillary diagnostic finding in some patients with sarcoidosis and may also confirm ongoing disease activity. Routine immunoglobulin estimation may disclose hypogammaglobulinaemia in undiagnosed granulomatous disorders but has no diagnostic value in other diffuse lung disorders.

Autoantibody testing is an essential part of routine evaluation. The presence of a positive antinuclear antibody, with specific extractable nuclear antigen profiles, or rheumatoid factor, may disclose an occult systemic rheumatological condition. The autoantibody profile is sometimes indicative of the likely pattern of pulmonary involvement. In systemic sclerosis: the anti-DNA topoisomerase autoantibody is often associated with clinically significant pulmonary fibrosis whereas the anticentromere antibody is linked to pulmonary vascular disease. The anti-t-RNA synthetase autoantibodies occur when polymyositis is associated with diffuse parenchymal lung disease. Other common associations include anti-Sm in systemic lupus erythematosus, SS-A, and SS-B in Sjögren's syndrome and the anti-RNP autoantibody in mixed connective tissue disease. Mild increases in antinuclear antibody and rheumatoid factor titres are commonly found in IPF and idiopathic fibrotic NSIP but appear to have no clinical significance. Increased antineutrophil cytoplasmic antibodies with a cytoplasmic pattern are strongly suggestive of Wegener's granulomatosis or microscopic polyangiitis. The perinuclear (pANCA) pattern is less discriminatory.

The presence of specific precipitins to organic antigens is often diagnostically useful in hypersensitivity pneumonitis. However, positive precipitins are not, in isolation, diagnostic, confirming only the presence of immunological recognition. Avian precipitins, for example, are often present in healthy pigeon breeders. Moreover, the absence of precipitins does not exclude a diagnosis of hypersensitivity pneumonitis: avian proteins causing disease in an individual may be species specific or, even, specific to a single bird.

Phase 2

High-resolution computed tomography

High-resolution computed tomography provides a three-dimensional anatomical reconstruction of both lungs, resulting in improved diagnostic accuracy, compared to chest radiography. Several HRCT patterns can now be viewed as pathognomonic and HRCT is often diagnostic in other patients when the findings are integrated with clinical information. The diagnostic use of HRCT essentially consists of an evaluation of the distribution and pattern of disease. A detailed review of the rapidly enlarging HRCT literature lies beyond the scope of this chapter and the reader is referred to sources listed in the 'Further reading' section.

HRCT is much more sensitive than chest radiography, leading to the earlier diagnosis of limited disease. While this is sometimes highly advantageous, the sensitivity of HRCT sometimes causes its own problems. The detection of limited abnormalities in cigarette smokers, or when HRCT is used as a screening tool in rheumatological disorders, sometimes leads to difficulty in assigning clinical significance to the findings. In this context, pulmonary function tests have a pivotal role but are sometimes difficult to interpret when functional impairment is minor, due to the wide normal range: a

forced vital capacity (FVC) of 75% of predicted can equally represent a minor fall or a major reduction from premorbid values of 80% and 120% of predicted, respectively. Absence of oxygen desaturation on maximal exercise testing is especially helpful in this scenario.

A simple HRCT diagnostic algorithm can be usefully be applied to apparently idiopathic diffuse lung disease. Confirmation of fibrosing disease is readily demonstrated by the presence of reticular abnormalities, anatomical distortion or, when ground-glass attenuation predominates, traction bronchiectasis. The essential preliminary question is whether HRCT appearances are typical of IPF (i.e. predominantly basal reticular abnormalities, with or without honeycombing, with little ground-glass attenuation). If not, it is appropriate to look for the HRCT features of fibrotic NSIP, sarcoidosis, hypersensitivity pneumonitis, and organizing pneumonia with fibrosis, disorders which, with IPF, account for up to 95% of diagnoses in apparently idiopathic disease. When HRCT appearances are not typical of one of these disorders and disease is progressive, IPF with atypical HRCT features is the most frequent diagnosis made at surgical biopsy.

HRCT has some other advantages. Even when the HRCT diagnosis is uncertain, the signs of fibrosis listed earlier often make it clear that disease is irreversible. The identification of reversible disease is less straightforward. Prominent ground-glass attenuation often denotes inflammation, but only when there is no admixed reticular pattern or traction bronchiectasis. HRCT is also invaluable in allowing the thoracic surgeon to select optimal sites for biopsy, by which means the full range of morphological abnormalities and disease severity can be sampled. Serial HRCT is sometimes useful in monitoring changes in disease severity, especially when pulmonary function trends are inconclusive, although HRCT should be used for this purpose in order to cast light on clinically important questions in individual patients and not performed rigidly by protocol.

Finally, HRCT is often revealing when disease processes are admixed. In rheumatological disorders and in smoking-related disease, patterns of functional impairment are often complex and an assessment of the extent of interstitial disease allows a better understanding of the presence and likely functional impact of emphysema and airway disease. The complications of diffuse lung disease are often disclosed by HRCT. Lung malignancy is increased in prevalence in fibrosing lung disease but can sometimes be difficult to detect on chest radiography when interstitial fibrosis is extensive. Infection is also sometimes masked in extensive disease, and this applies especially to aspergillomas, which tend to develop in fibrobullous sarcoidosis.

Bronchoalveolar lavage

When first employed, it was hoped that BAL might replace diagnostic surgical biopsy or provide accurate prognostic information, and that serial BAL might disclose important changes in disease activity. Further evidence did not support these expectations, and the role of BAL has now been down-graded. However, BAL has an ancillary diagnostic role in diffuse lung diseases and is also sometimes helpful in excluding infection. Granulomatous and drug-induced lung diseases are characterized by an excess of lymphocytes with or without granulocytes. The presence of a BAL lymphocytosis is occasionally pivotal in alerting the clinician to the possibility that a fibrosing process may be due to hypersensitivity pneumonitis or sarcoidosis. Bronchoalveolar lavage can also be diagnostic in some rare lung disorders, including alveolar proteinosis (milky effluent; PAS-positive material), Langerhans cell histiocytosis (increased numbers of Langerhans cells identified by CD1a staining), alveolar haemorrhage (iron-laden macrophages) and hard metal lung disease (bizarre multinuclear giant cells). By contrast, a BAL neutrophilia is an expected finding when pulmonary fibrosis is moderately extensive and has little diagnostic value, particularly where clinical and HRCT evaluation are characteristic of IPF. It appears increasing likely, based on recent data, that the observed linkage between disease progression and a BAL neutrophilia in rheumatological disease reflects the presence of more severe disease, which is, itself, more likely to progress.

BAL is an essential part of the diagnostic algorithm in patients presenting acutely with widespread interstitial abnormalities. Diffuse alveolar haemorrhage does not always manifest with haemoptysis but is readily disclosed by BAL. In patients receiving immunosuppressive drugs, increased treatment may be urgently required in the hope of reversing disease progression. However, acute decompensation due to opportunistic infection may be excluded more confidently only with BAL.

Lung biopsy

Assessment of a surgical lung biopsy offers the important advantage that further investigation is unlikely to clarify the situation and a final diagnosis must now be made, integrating all clinical, radiological, and histological information. A confident diagnosis leads to more confident management, with a more accurate evaluation of the balance of risk and benefit with suggested treatments. Clinicians are better able to inform the patient of the likely natural history and treated course of disease. In many patients, a firm diagnosis can be made from clinical and HRCT data, and a surgical biopsy is redundant. In other cases, a biopsy is contraindicated by advanced age, the severity of disease, major comorbidity, or the wishes of the patient. The acquisition of biopsies from more than one lobar site increases the likelihood of obtaining representative tissue. The limited thoracotomy approach used historically has now been supplanted by video-assisted thoracoscopic surgical procedures, which are less invasive, provide equivalently sized samples and are associated with less morbidity.

The morbidity and mortality associated with diagnostic surgical biopsy are low provided that pulmonary reserve is adequate. However, postoperative mortality increases significantly when disease is extensive and exceeded 15% in one IPF series in which the average level of functional impairment were severe. Thus, if the DL_{CO} level is less than 35% of predicted, a surgical biopsy should be performed only if considered indispensable. The histological diagnosis is, in any case, less prognostically useful in advanced disease. Mortality is very similar in IPF and fibrotic NSIP when DL_{CO} levels are less than 35%, despite striking differences in survival when disease is less severe.

Transbronchial lung biopsies

Transbronchial lung biopsies (TBLB) are most useful in diagnosing airway-centred disorders. In sarcoidosis and lymphangitis carcinomatosis, the histological appearances are sufficiently characteristic to allow a confident diagnosis to be made from very small biopsy specimens. However, for most diffuse lung diseases, including the idiopathic interstitial pneumonias, their morphological complexity

renders the overall pattern of disease difficult to meaningfully evaluate without a larger surgical biopsy.

Over the recent years, transbronchial lung cryobiopsy (TBLC) has emerged as a promising new technique in the diagnostic evaluation of diffuse parenchymal lung disease. Originally developed to treat endobronchial tumours, TBLC confers the advantage of being able to harvest larger and architecturally better-preserved pieces of lung parenchymal tissue compared to TBLB. Several studies have reported improved diagnostic yield with TBLC compared to conventional TBLB; this enabled a definitive histological pattern to be identified with a high level of confidence in significantly more samples harvested by TBLC than TBLB. Whether this translated to a change of initial consensus at diagnosis or enabled the multidisciplinary team to reach a definitive diagnosis is less clear. Safety issues are also a concern, namely, a higher risk of significant bleeding, and to a lesser extent, pneumothorax, with TBLC. It was also noted that most studies excluded patients with a DLCO of less than 35%, where surgical lung biopsy might have been contraindicated, thus not offering an advantage in this respect to patients with marginal lung function. At present, surgical lung biopsy remains the gold standard procedure for obtaining a histological diagnosis in diffuse parenchymal lung disease but the reader is alerted to the possibility that TBLC may supplant surgical biopsy in the near future as more data are rapidly accumulated.

Transbronchial needle aspiration

In patients with suspected stage I and II sarcoidosis, transbronchial needle aspiration (TBNA) of intrathoracic lymph nodes by conventional TBNA or endosonography (endobronchial or oesophageal ultrasound -guided) may be a useful tool in detecting the presence of noncaseating granulomas. In the largest yet multicentre randomized control trial comparing the diagnostic yield of bronchoscopy (with transbronchial or endobronchial mucosal biopsy) vs. endosonography for stage I and II sarcoidosis, the use of endosonographic nodal aspiration compared with bronchoscopic biopsy resulted in a greater yield (80% vs. 53%) with an equivalent safety profile.

Key clinical issues

Integrated diagnosis

Although a histological diagnosis made at surgical biopsy was once viewed as definitive in diffuse parenchymal lung disease, it is now widely accepted that all clinical, radiological, and histopathological data must be integrated into the final diagnosis. The limitations of a histological diagnosis are now better understood. 'Sampling error' consists of the acquisition of nonrepresentative tissue: in some patients with IPF, there are lung regions with the histological appearances of fibrotic NSIP, but this finding has no prognostic significance. Sampling error can be minimized by ensuring that large samples are taken, by sampling more than one site, and by selecting the sites of biopsy to sample the full range of disease morphology and severity, based on HRCT appearances. However, diagnostic variation between pathologists remains problematic, with less agreement than documented with many clinically useful tests. Moreover, in some cases, there is 'appropriate' interobserver variation, reflecting the fact that histological appearances occasionally lie intermediate between classical entities. To complicate matters further, the diagnostic significance of a histological pattern is critically dependent upon the clinical context. For example, usual interstitial pneumonia is the required histological pattern in IPF but sometimes has a better outcome when occurring in patients with rheumatological disorders, drug-induced lung disease, or hypersensitivity pneumonitis.

Thus, the gold standard for diagnosis in diffuse parenchymal lung disease is now a multidisciplinary diagnosis, with participation by clinicians, radiologists and, when applicable, histopathologists. As a useful rule of thumb, in nonbiopsied cases the clinical and HRCT evaluation is, on average, equally influential, and careful clinical assessment should not be curtailed because of the ready availability of HRCT. In patients undergoing surgical biopsy, clinical and HRCT findings are usually inconclusive and the histological features tends to carry the most diagnostic weight. However, it is accepted that the final diagnosis should differ from the histological diagnosis in a significant minority of patients, when all available information is integrated.

The principles of management

The chronic diffuse parenchymal lung diseases can be broadly subclassified into five patterns of longitudinal disease behaviour, based upon cause, severity, the relative degree of inflammation and fibrosis, and observed change in the short term. Each clinical pattern is associated with a separate approach to management.

1. *Reversible and self-limited disease* is usually caused by an extrinsic agent (as in drug-induced disease, hypersensitivity pneumonitis and RB-ILD) but may also be idiopathic as in a subset of patients with sarcoidosis. Disease usually responds to withdrawal of an offending agent, therapy is often unnecessary, and monitoring consists of confirming that disease has regressed.
2. *Reversible major disease with risk of progression, with or without supervening fibrosis* is often a feature of drug-induced lung disease and this category also applies to some patients with cryptogenic organizing pneumonia, DIP, cellular and some fibrotic NSIP, hypersensitivity pneumonitis, and sarcoidosis. High-dose therapy is usual, often with corticosteroids, and the short-term response is quantified, often at four to six weeks. Once inflammation is controlled and the residual level of functional impairment has been quantified, treatment is gradually reduced with monitoring centred around serial pulmonary function tests, usually at three to four monthly intervals. In this way, the minimum dose required to maintain control of disease is established.
3. *Residual but stable fibrotic disease* is most commonly encountered in sarcoidosis, following drug-induced lung disease, and in patients with formerly active rheumatological disorders. Treatment is not required but long-term monitoring is needed to ensure that disease is truly stable, usually with serial pulmonary function tests until a long-term 'track record' of disease stability has been established.
4. *Progressive fibrotic disease, in which stabilization is a realistic goal,* is frequently seen in sarcoidosis, hypersensitivity pneumonitis, rheumatological conditions, and in many patients with fibrotic NSIP. In this scenario, long-term therapy is often required and long-term monitoring with serial pulmonary function tests, often at increasing time intervals, is needed to ensure

that stabilization has been achieved and maintained. Aggressive initial treatment is usually warranted to ensure optimal control of disease activity.

5. *Inexorably progressive fibrotic disease* is the hallmark of IPF, but an IPF-like course is sometimes observed in idiopathic fibrotic NSIP, rheumatological disease, and in a small subset of patients with chronic hypersensitivity pneumonitis. Long-term treatment may slow disease progression and reduce mortality, as evidenced by recent data on anti-IPF specific therapies (such as pirfenidone and nintedanib—discussed further in Chapter 18.11.2). The early realization that fibrotic disease may be relentlessly progressive, either because IPF is diagnosed or because disease continues to progress despite treatment, is especially important when lung transplantation or, in cases where this may not be possible, effective palliation, is realistic. Monitoring is performed to quantify disease progression, usually at three to four monthly intervals.

This schema is proposed in order to capture key thought processes of clinicians and to serve as a rationale for treatment and monitoring decisions. In many cases, the pattern of disease behaviour is evident at presentation, but careful short-term observation is highly informative in other instances.

When should a surgical biopsy be performed?

A broad classification of disease behaviour also serves as a rationalization of when to recommend a diagnostic surgical biopsy. When the underlying diagnosis is uncertain and the clinician is unable to assign likely disease behaviour, and therefore management is diffident, a surgical biopsy is usually warranted (age, disease severity, and comorbidity permitting). However, if the diagnosis is uncertain but the pattern of disease behaviour is already clear, a diagnostic biopsy is much less likely to inform management. For example, when it is already known from previous investigations that fibrotic abnormalities are long-standing and wholly stable, a histological diagnosis is unlikely to change management.

When considering whether or not to recommend biopsy, it is useful to construct scenarios in which long-term management may differ significantly depending upon histological findings. It is important to reach an early decision. The empirical approach of initiating treatment, with recourse to biopsy if the response is unsatisfactory, has serious flaws. Modification of the histological appearances by treatment may make diagnosis more difficult and, more importantly, deterioration during the interim period may make the biopsy more hazardous, as well as increasing the likelihood of side effects to treatment, including postoperative infection and impaired wound healing. Thus, the best time to perform a biopsy is shortly after presentation, before treatment is instituted.

FURTHER READING

BAL Co-operative Group Steering Committee (1990). Bronchoalveolar lavage constituents in healthy individuals, idiopathic pulmonary fibrosis, and selected comparison groups. *Am Rev Respir Dis*, **141**, S169–S202.

Bjoraker JA, *et al.* (1998). Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*, **157**, 199–203.

Bradley B, *et al.* (2008). Interstitial lung disease guidelines: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax*, **63**, Suppl. 5, v1–v58.

Desai SR, Wells AU (2007). Imaging. In: Costabel U, du Bois RM, and Egan JJ (eds). *Diffuse parenchymal lung disease*, pp. 29–43. Karger, Basel.

Flaherty KR, *et al.* (2001). Histologic variability in usual and nonspecific interstitial pneumonias. *Am J Respir Crit Care Med*, **164**, 1722–7.

Flaherty KR, *et al.* (2004). Idiopathic interstitial pneumonia. What is the effect of a multi-disciplinary approach to diagnosis? *Am J Respir Crit Care Med*, **170**, 904–10.

Joint American Thoracic Society and European Respiratory Society Group (2000). Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med*, **161**, 646–64.

Joint American Thoracic Society and European Respiratory Society Group (2002). International multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*, **165**, 277–304.

Joint American Thoracic Society and European Respiratory Society Group (2013). Update of the international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*, **188**, 733–48.

Katzenstein AL, Myers JL (1998). Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. *Am J Respir Crit Care Med*, **157**, 1301–15.

Liebow AA (1975). Definition and classification of interstitial pneumonias in human pathology. In: Basset F, Georges R (eds). *Progress in respiration research*, pp. 1–33. Karger, New York.

Muller NL, Colby TV (1997). Idiopathic interstitial pneumonias: high-resolution CT and histologic findings. *Radiographics*, **17**, 1016–22.

Nicholson AG, *et al.* (2004). Inter-observer variation between pathologists in diffuse parenchymal lung disease. *Thorax*, **59**, 500–5.

Nicholson AG, *et al.* (2000). The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med*, **162**, 2213–17.

Pajares V, *et al.* (2014). Diagnostic yield of transbronchial cryobiopsy in interstitial lung disease: a randomized trial. *Respirology*, **19**, 900–6.

Reddy TL, *et al.* (2012). Pleuroparenchymal fibroelastosis: a spectrum of histopathological and imaging phenotypes. *Eur Respir J*, **40**, 377–85.

von Bartheld MB, *et al.* (2013). Endosonography vs conventional bronchoscopy for the diagnosis of sarcoidosis: the GRANULOMA randomized clinical trial. *JAMA*, **309**, 2457–64.

Wells AU (2003). High resolution computed tomography in the diagnosis of diffuse lung disease: a clinical perspective. *Semin Respir Crit Care Med*, **24**, 347–56.

Wells AU (2004). Histopathologic diagnosis in diffuse lung disease: an ailing gold standard. *Am J Respir Crit Care Med*, **170**, 828–9.

Wells AU, Hansell DM, Nicholson AG (2007). What is this thing called CFA? *Thorax*, **62**, 3–4.

18.11.2 Idiopathic pulmonary fibrosis

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ESSENTIALS

The synonymous terms idiopathic pulmonary fibrosis and cryptogenic fibrosing alveolitis refer to a relentlessly progressive fibrotic lung disorder. Incidence is about 5 to 15 per 100 000, men are more often affected than women, and it most commonly presents in the seventh and eighth decades. Aetiology remains uncertain.

Clinical features—typical presentation is with progressive exertional dyspnoea without wheeze, a nonproductive cough, digital clubbing, and very fine end-inspiratory crackles. Central cyanosis and clinical evidence of pulmonary hypertension are late features.

Diagnosis—depends on careful exclusion of known causes of interstitial lung disease, followed by demonstration by radiological imaging or biopsy of the pathognomonic lesion of usual interstitial pneumonia.

Management—two antifibrotic compounds, pirfenidone and nintedanib, have been proven to slow functional decline in idiopathic pulmonary fibrosis. Treatments that target inflammation (e.g. corticosteroids and immunosuppressive agents) are generally of no benefit and may do harm, although acute exacerbations, which affect 10–15% of patients each year and are often fatal, are typically given a trial of high-dose corticosteroid. Lung transplantation is appropriate in selected cases. Supportive therapy is central to the management of advanced disease. Five-year survival is 10–15%.

Introduction

The disorder previously known as fibrosing alveolitis, first described in 1907, was increasingly recognized following the description of a small group of patients with rapidly progressive fatal disease, grouped as the Hamman–Rich syndrome. Until late in the twentieth century, a stereotypical clinical presentation of idiopathic interstitial lung disease was termed idiopathic pulmonary fibrosis (IPF) or cryptogenic fibrosing alveolitis (CFA), with several histological patterns unified under this term. However, it became increasingly clear that the clinical presentation of IPF/CFA ('CFA clinical syndrome') was shared by diseases including predominantly inflammatory and predominantly fibrotic disorders, now known collectively as the idiopathic interstitial pneumonias. Their separation is essentially pragmatic, justified by large differences in treated outcome.

The new classification proposed by an American Thoracic Society/European Respiratory Society nomenclature committee is now widely accepted and can be readily applied to routine practice, with increasing recognition of characteristic patterns of disease on high resolution computed tomography (HRCT). Histological evaluation tends to be reserved for the few patients in whom best management cannot be based on clinical and HRCT findings. The synonymous terms IPF and CFA now refer to a relentlessly progressive fibrotic disorder, associated with a histological pattern of usual interstitial pneumonia (UIP) or typical HRCT and clinical features in nonbiopsied cases.

Epidemiological and aetiological data are briefly reviewed and the clinical picture is summarized. Key clinical issues are then discussed, including diagnosis, prognostic evaluation, routine monitoring, and treatment.

Epidemiology and aetiology

IPF most commonly affects men, rarely presents before the age of 50, and exhibits considerable geographic variation. The incidence and prevalence have risen steadily in recent decades, with the incidence now likely to approximate 10–15 per 100 000, based upon evaluation of death certificates and registry studies in the United States, United Kingdom, and elsewhere. A recent study, using case definitions more reliably indicative of IPF, has suggested an incidence of 5 to 10 per 100 000.

The pathogenesis of IPF remains unknown. It was historically considered that inflammation preceded fibrosis, but the paucity of evidence of inflammation in histopathological samples and the lack of efficacy of immunosuppressive therapy led to a shift in thinking. Current evidence suggests IPF develops in genetically susceptible individuals with dysfunctional alveolar epithelial repair mechanisms following repeated episodes of alveolar injury. Repetitive injury results in myofibroblast recruitment and activation, and collagen deposition causing progressive accumulation of scar tissue, resulting in the classical radiological and histological patterns of UIP. Destruction of the lung architecture causes loss of alveolar structure, impairing gas exchange and ultimately resulting in respiratory failure. The presumptive model of development therefore suggests a role in IPF for both host and environmental factors, with interactions between the two in all likelihood.

Environmental factors

Several environmental triggers have been suggested as plausible causative factors, but as yet the initial stimulus remains unidentified. A history of smoking is associated with an increased risk of developing both the familial and sporadic forms of IPF, but cigarette smoke alone cannot be the only trigger as the disease also occurs in nonsmokers. Epidemiological studies have also implicated environmental and occupational exposures to metal dusts and wood fires, which confer an increased risk of IPF.

Genetic factors

Familial forms of IPF, where two or more members of a family are affected, provide strong evidence for an underlying genetic component to the disease. Familial forms of fibrosis have been linked to variants in the genes encoding two surfactant proteins (*SFTPC* & *SFTPA2*), genes that maintain telomere length (*hTERT* and *TERC*), and most recently the mucin 5B (*MUC5B*) gene.

The strongest and most reproducible genetic association with IPF to date is that of the mucin 5B (*MUC5B*) gene: a polymorphism (*rs35705950)* in its promoter region is associated with the development of both sporadic and familial IPF. Subjects carrying the mutation demonstrate an increased expression of MUC5B in the lung, which accumulates within areas of honeycombing. This association has now been robustly replicated and the association with *MUC5B* was also the dominant finding in two recent genome-wide association studies.

The mucin glycoproteins are a major structural component of the mucus barrier, maintaining the hydration of the airway epithelium and crucially entrapping particles for removal by mucociliary clearance. This has led to the hypothesis that excess production of MUC5B reduces mucociliary clearance of inhaled particles, resulting in prolonged and repetitive exposure, triggering an exaggerated interstitial injury, and eventually leading to the development of fibrosis.

Diagnostic criteria

The publication of the ATS, ERS, JRS, and ALAT joint statement on IPF in 2011 marked a significant shift in the diagnostic paradigm for IPF. The major/minor diagnostic criteria set out in previous guidelines were eliminated, and more emphasis was placed on the multidisciplinary approach to diagnosis. The role and importance of surgical lung biopsies in the diagnostic process was also re-visited, given the emerging wealth of data regarding the specificity for the recognition of the histopathologic UIP pattern on HRCT. These 2011 diagnostic guidelines were revised and updated in 2018.

The suggested diagnostic pathway (Fig. 18.11.2.1) starts with careful exclusion of known causes of interstitial lung diseases. This is achieved through a thorough history, examination, and serological testing to identify predisposing domestic and occupational environmental exposures, and underlying medical conditions. A detailed family history is also necessary as some estimates suggest that up to 10% of cases of IPF are familial.

If no underlying cause can be identified the patient may have IPF, and evidence of the pathognomonic lesion of UIP is sought, initially radiologically. The 2018 guidelines clearly state the precise HRCT features that meet the criteria for 'UIP', 'probable UIP pattern', 'indeterminate for UIP pattern' and 'alternative diagnosis'. In the appropriate clinical setting, satisfaction of HRCT criteria for a pattern of UIP obviates the need for further investigations such as cellular analysis of bronchoalveolar lavage (BAL) fluid, transbronchial biopsy or surgical lung biopsy. By contrast, cellular analysis of bronchoalveolar lavage (BAL) fluid or surgical lung biopsy should be considered when the diagnosis is thought to be probable UIP, indeterminate for UIP or an alternative diagnosis. The weight of combined clinical, histopathological, and radiological information is then used by a multidisciplinary team to confirm or refute a diagnosis of IPF (Table 18.11.2.1).

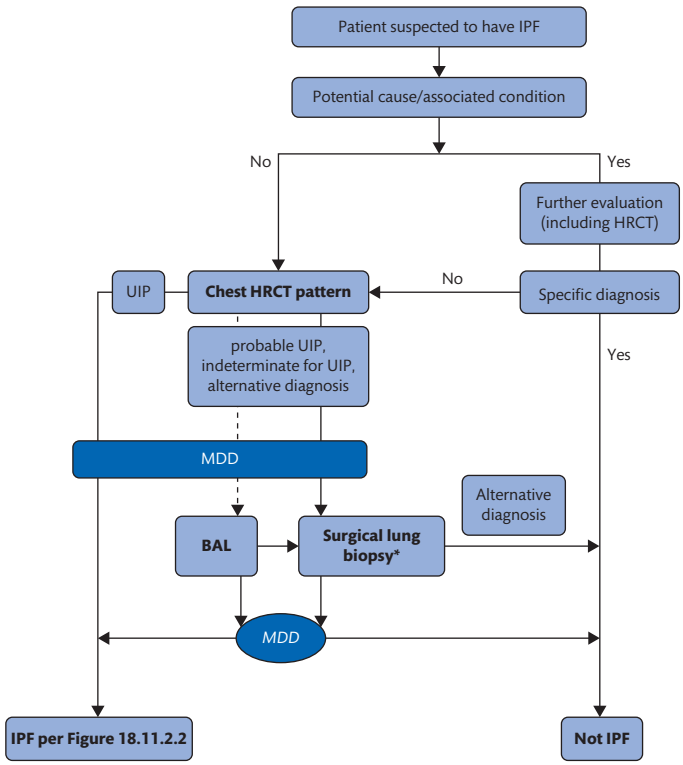

Fig. 18.11.2.1 Diagnostic algorithm for idiopathic pulmonary fibrosis (IPF). If a patient is suspected of having IPF but a specific diagnosis is not made or no potential cause for interstitial lung disease (ILD) is identified, further evaluation depends on the appearances of high resolution CT images (HRCT) of the chest and clinical input from multidisciplinary discussion (MDD). IPF is diagnosed if the appropriate combination of HRCT patterns and histopathological patterns are present (see Table 18.11.2.1).

From Raghu G, *et al*. (2018). Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*, **198**, e44–e68.

Histological features and pathogenesis

In UIP, the histological pattern underlying IPF (Fig 18.11.2.2), temporal and spatial heterogeneity of disease is the cardinal feature. Normal lung is seen adjacent to regions of fibrosis, with enlarged cystic air-spaces (honeycomb lung) and areas of milder interstitial fibrosis. A patchy chronic inflammatory cell infiltrate is variably present. Subepithelial foci of proliferating fibroblasts ('fibroblastic foci') are a characteristic feature, occurring occasionally and sparsely in nonspecific interstitial pneumonia (NSIP) but not seen in other idiopathic interstitial pneumonias.

Historically, it was believed that inflammation was the key pathogenetic process, preceding and leading to fibrotic disease, but this view has been largely abandoned. Corticosteroid and immunosuppressive therapy, effective in primary inflammatory disorders, have now been shown in large studies to confer no treatment benefit. Indeed, far from demonstrating any benefit, immunosuppression has actually proven to be harmful in IPF.

There is increasing evidence that IPF has an epithelial fibrotic pathogenesis, with initial epithelial damage leading to the formation of fibroblastic foci and subsequently to more widespread thickening of the connective tissue matrix in advanced disease. Thus, IPF can be conceptualized as a disorder of abnormal wound healing. In established disease, lung injury, an immunological and inflammatory response, and fibrogenesis appear to occur in parallel. It is not known whether a single key mechanism is pivotal in pathogenesis. Oxidant-antioxidant imbalance and the release of damaging enzymes from inflammatory cells appear to amplify injury, but a wide variety of biological mechanisms interact in the lungs of patients with IPF, with up-regulation of tumour necrosis factor-α and chemokines (interleukin 8, and growth factors, especially transforming growth factor-β; and connective tissue growth factor), and activation of the coagulation cascade, known to promote fibrogenesis. However, it is not clear whether these mechanisms are primarily pathogenetic or represent physiological responses to an up-stream abnormality. The profusion of fibroblastic foci and

Table 18.11.2.1 Idiopathic pulmonary fibrosis (IPF) based upon HRCT and biopsy patterns

IPF suspected[a]		Histopathology pattern			
		UIP	Probable UIP	Indeterminate for UIP	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)[b]	Non-IPF dx
	Indeterminate for UIP	IPF	IPF (Likely)[b]	Indeterminate for IPF[c]	Non-IPF dx
	Alternative diagnosis	IPF (Likely)[b] /non-IPF dx	Non-IPF dx	Non-IPF dx	Non-IPF dx

[a] Clinically suspected of having IPF.
[b] IPF is the likely diagnosis when any of the following features are present: (1) moderate-to-severe traction bronchiectasis/bronchiolectasis in a man >50 years or woman >60 years; (2) >30% reticulation on HRCT at age >70 years; (3) increased neutrophils and/or absence of lymphocytosis in BAL fluid; (4) multidisciplinary discussion makes confident diagnosis of IPF.
[c] Indeterminate for IPF—without adequate biopsy is unlikely to be IPF; with adequate biopsy may be reclassified.
Source data from Raghu G, *et al.* (2018). Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*, 198, e44–e68.

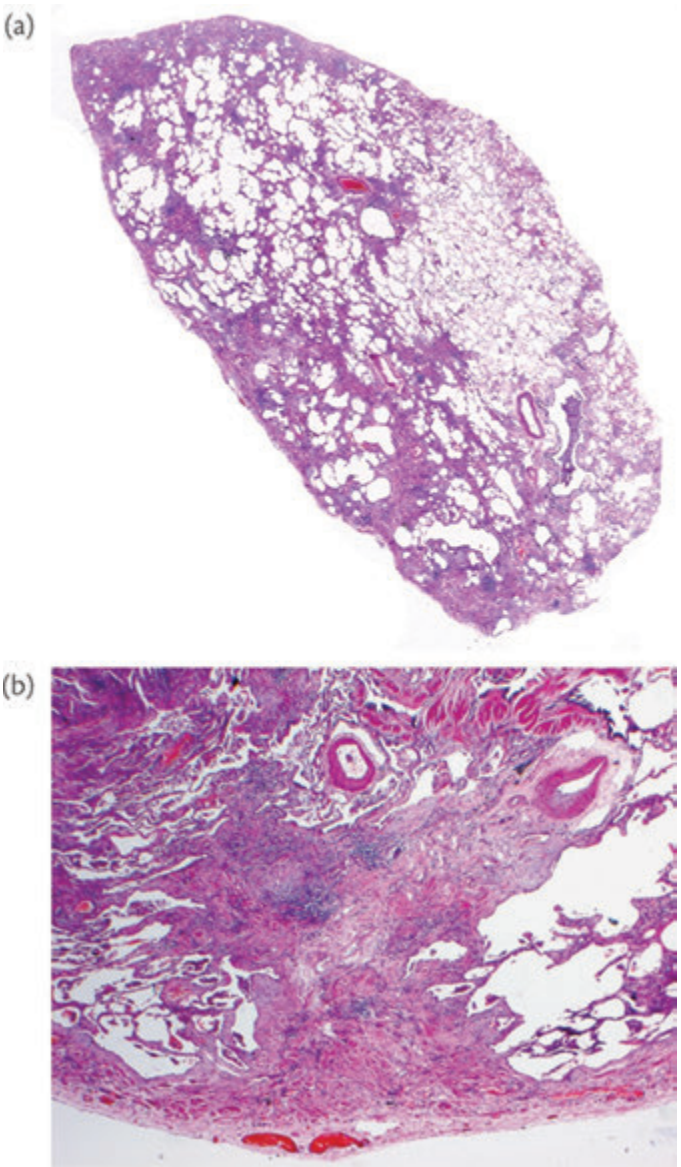

Fig. 18.11.2.2 (a) Surgical lung biopsy from a patient with IPF shows a patchy established fibrosis with a predominantly subpleural distribution. (b) At high power there is a mild degree of associated nonspecific chronic inflammation with fibroblastic foci in continuity with the established fibrosis. Note the relatively sharp demarcation between normal and abnormal parenchyma.

serum levels of protein markers of epithelial damage have both been linked to mortality and disease progression.

Clinical features

The typical presentation is progressive exertional dyspnoea without wheeze and a nonproductive cough, although sputum production is present in a minority of patients. Haemoptysis should prompt investigation for lung malignancy, which is approximately 10-fold more prevalent in IPF, after the smoking history has been taken into account. Chest discomfort, fatigue, and weight loss are occasional features. Digital clubbing is present in over 50% of patients and has been an adverse prognostic determinant in some series. On auscultation, very fine end-inspiratory crackles are typical heard bilaterally at the lung bases and become widespread in advanced disease. Central cyanosis and clinical evidence of pulmonary hypertension, with or without right ventricular failure, are late features.

Investigation

Chest radiography

The chest radiograph typically shows small lung volumes and predominantly peripheral and basal reticulonodular shadowing, with obscuration of the heart borders and diaphragms in advanced disease and overt honeycombing in 10% of cases. This profile is highly nonspecific, occurring in fibrotic NSIP, asbestosis, rheumatological disorders, and other fibrotic processes. Lymphadenopathy or pleural disease should suggest an alternative diagnosis or a concurrent pathological process. Cardiomegaly may occur in the absence of cardiovascular disease as a result of reduced intrathoracic volume.

High resolution computed tomography

HRCT appearances are virtually pathognomonic in up to 60% of patients (Fig. 18.11.2.3). The disease is predominantly postero-basal and peripheral, becoming widespread in advanced disease, and consists of a reticular pattern, with or without honeycombing, and a minor component of ground-glass attenuation, usually indicative of fine fibrosis (rather than inflammation). It should be stressed that HRCT appearances are atypical in at least 40% of cases, with the most frequent variant consisting of prominent ground-glass

Fig. 18.11.2.3 HRCT scan of a patient with biopsy-proven IPF. Appearances are typical of IPF with a subpleural distribution of microcystic and macrocystic honeycomb change.

attenuation admixed with a fine reticular pattern and associated with traction bronchiectasis: an appearance also suggestive of NSIP (Fig. 18.11.2.4). However, IPF is also diagnosed (i.e. a histological pattern of UIP at biopsy) in occasional patients with markedly atypical HRCT appearances (Fig. 18.11.2.5 a, b). Reactive mediastinal lymphadenopathy is usual on HRCT and is not indicative of a coexisting disease process unless also present on chest radiography. In early disease, prone HRCT sections may be required to distinguish abnormal appearances from normal increases in density due to gravity-related increases in perfusion in dependent areas.

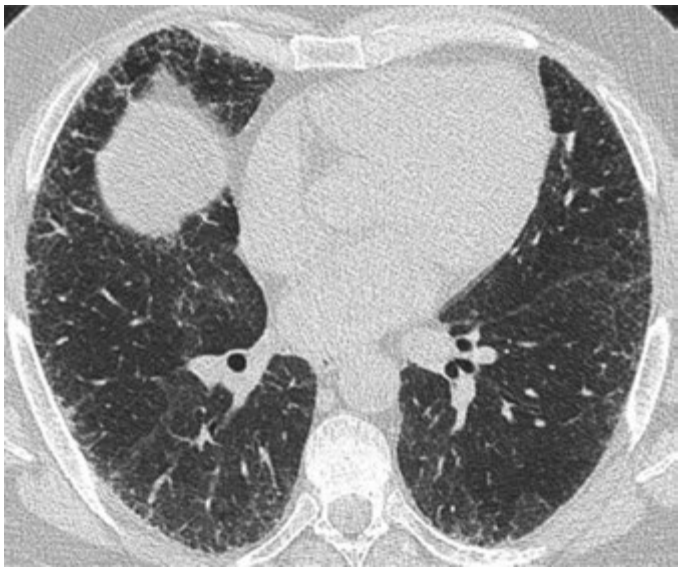

Fig. 18.11.2.4 HRCT scan of a patient with biopsy-proven IPF showing abnormalities that overlap in appearance with those seen in nonspecific interstitial pneumonia. Disease is predominantly subpleural but consists of a mixture of ground-glass attenuation and fine reticular abnormalities, without honeycombing. This appearance is seen in a significant minority of IPF patients.

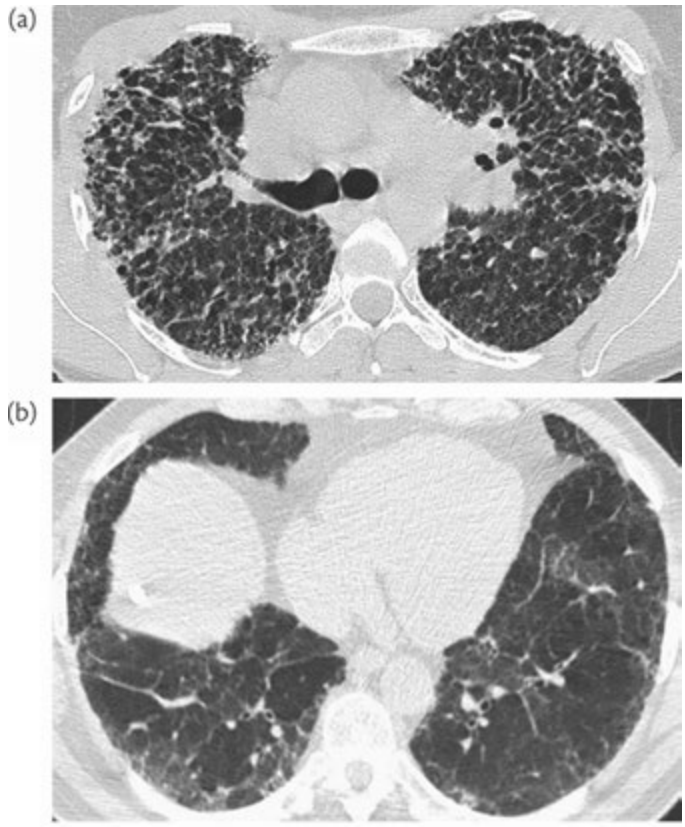

Fig. 18.11.2.5 (a and b) HRCT scans in patients with biopsy-proven IPF, but in both cases the HRCT appearances are markedly atypical, with no features indicative of IPF or of any other form idiopathic interstitial pneumonia. IPF should always be suspected when disease is inexorably progressive and HRCT appearances are difficult to classify.

Other imaging modalities

Ventilation–perfusion scans show ventilation mismatch due to vascular ablation in areas of cystic lung, which typically continue to ventilate normally. These appearances simulate pulmonary thromboembolism and probably account for a widespread misperception that pulmonary embolism is a frequent complication of IPF. CT pulmonary angiography is required when pulmonary embolism is suspected, especially when DLco levels are disproportionately reduced, but is usually negative in this context.

Lung function tests

Lung function tests reveal a restrictive ventilatory defect, as shown by reductions in vital capacity, total lung capacity, residual volume, and pulmonary compliance. However, the wide range in normal premorbid lung volumes sometimes results in apparent normality (when lung volumes have fallen from the upper to the lower end of the normal range). Thus, measures of gas transfer, especially DLco levels, may be reduced in isolation in early disease. Adjustment of DLco for reduced alveolar volume (*K*co) has been advocated, as a more specific index of interstitial fibrosis, but Kco levels are disproportionately reduced by coexistent emphysema, which is present in over 30% of IPF patients. The combination of emphysema and IPF may result in spurious preservation of lung volumes, even

in advanced disease, and disproportionate reduction in DLco levels. Overall, the severity of disease is most accurately captured by DLco levels, which correlate best with the extent of IPF, as judged by HRCT findings. In early disease, arterial gases may be normal but mild arterial hypoxia with widening of the alveolar-arterial gradient and normal or low $Paco_2$ levels are usual. Severe hypoxia is a late feature and increased $Paco_2$ levels occur in terminal disease.

Blood tests

Blood tests contribute little to the management of IPF, except in rare cases in which an unsuspected underlying cause is identified. Mild increases in the erythrocyte sedimentation rate, serum immunoglobulins, rheumatoid factor, and antinuclear antibodies are frequent and in severe disease, secondary polycythaemia may occur. A high neutrophil count may be indicative of infection but a moderate increase is also seen in association with corticosteroid therapy. However, striking increases in autoantibodies may be indicative of a hitherto undiagnosed rheumatological disorder. Precipitin tests against fungal and avian antigens should be performed when there is suggestive exposure history, as chronic extrinsic allergic alveolitis occasionally presents with HRCT appearances suggestive of IPF and a pattern of UIP at surgical biopsy.

Bronchoalveolar lavage

Bronchoalveolar lavage is a useful ancillary diagnostic test when a surgical biopsy is not performed. Typically, there is an increase in total cell counts and an excess of neutrophils and/or eosinophils is usual. A mild lymphocytosis is not infrequent but striking rises in lymphocyte counts are not generally a feature of IPF and suggest an alternative disorder such as NSIP, hypersensitivity pneumonitis, fibrotic sarcoidosis, cryptogenic organizing pneumonia complicated by interstitial fibrosis or drug-induced lung disease. Bronchoalveolar lavage is occasionally useful in excluding opportunistic infection in treated patients.

Echocardiography

Based upon recent reports of a high prevalence of pulmonary hypertension in IPF, routine echocardiography is warranted at presentation and in patients subsequently developing disproportionate hypoxia or a selective serial reduction in DLco. In some IPF patients, the development of pulmonary hypertension is a feature of end-stage disease, but in other cases, early pulmonary hypertension occurs, not associated with major functional impairment due to interstitial lung disease.

Surgical lung biopsy

A surgical lung biopsy is the histological diagnostic procedure of choice. Video-assisted thoracoscopic biopsy is the most widely used procedure but mini-thoracotomy is occasionally required in advanced disease. It is strongly recommended that at least two sites are biopsied and HRCT findings should be taken into account to ensure that the full spectrum of morphological abnormalities is sampled, and to avoid areas of end-stage disease which seldom yield diagnostic tissue. The diagnosis of IPF and other idiopathic interstitial pneumonias cannot be based upon appearances at transbronchial biopsy, as larger biopsies are required to determine whether abnormalities are spatially heterogeneous or truly homogeneous (as in NSIP), a crucial discriminatory diagnostic feature.

Diagnosis

Once suspected in the symptomatic patient, IPF is usually easy to detect using lung function tests and chest radiography, but in early disease HRCT be required to confirm or exclude interstitial lung disease. However—as discussed earlier—clinical, chest radiographic features and physiological features are highly nonspecific in discriminating between individual idiopathic interstitial pneumonias, and HRCT plays a crucial role in this regard. In most patients with IPF, HRCT appearances are diagnostic in an appropriate clinical setting and it is seldom necessary to confirm the diagnosis with invasive techniques, especially when a typical course of relentless progression is already apparent. However, in a significant number of patients diagnostic imprecision leads to major prognostic and management uncertainties, and brochoalveolar lavage and/or a diagnostic surgical lung biopsy is warranted. Thus, these investigations should not be performed by protocol in all cases but should be reserved for situations in which it appears realistic that clinician perceptions of best management, including treatment and the approach to monitoring, might change significantly with the addition of additional information.

In less typical cases, findings at bronchoalveolar lavage may play an important ancillary role in excluding alternative disorders such as hypersensitivity pneumonitis and respiratory bronchiolitis with associated interstitial lung disease (characterized by a striking lymphocytosis and a marked increase in pigmented macrophages, respectively).

It should be stressed that the distinction between IPF and fibrotic NSIP (discussed in Chapter 18.11.1), based upon clinical and HRCT features, poses particular difficulty. Even when HRCT appearances are considered typical for NSIP, there is a significant likelihood that a surgical biopsy will disclose a pattern of UIP, indicative of a worse outcome. In difficult cases it is essential to review the diagnosis in a multidisciplinary meeting, with the reconciliation of clinical and radiological features, in order to confirm that a diagnostic surgical biopsy is truly required. This decision is often difficult when IPF is likely, due to patient age (typically advanced), disease severity, and the presence of comorbidity, especially cardiovascular disease. The threshold for performing a biopsy is increased in patients aged over 65 years and when DLco levels are less than 35% of predicted, as both factors are associated with a significant increase in morbidity and the latter with an increase in exacerbations following biopsy.

It is also important that histological findings are no longer viewed as a diagnostic 'gold standard' in interstitial lung disease, although usually more diagnostically influential than clinical and HRCT features when the diagnosis is uncertain. A multidisciplinary diagnosis, made by negotiation between clinicians, radiologists, and pathologists, is now considered optimal. A histological pattern other than UIP is considered to exclude IPF, with one important caveat: 'sampling error' (i.e. a biopsy taken from a nonrepresentative site) should be kept in mind when HRCT findings and the subsequent clinical course are strongly suggestive of IPF. Conversely, when UIP is disclosed at biopsy, the final consensus diagnosis sometimes differs from the histological diagnosis. This applies

especially to patients with clinical evidence of hypersensitivity pneumonitis or a rheumatological disorder.

Prognostic evaluation

Accurate diagnosis is central to prognostic evaluation. The five-year survival approximates 10–15% in IPF, as compared to over 60% in fibrotic NSIP and over 90% in patients with predominantly inflammatory idiopathic interstitial pneumonias. Until recently it was believed that all patients exhibited a gradual but relentless decline in lung function reflecting the development of progressive fibrosis. However, the clinical course of individual patients with IPF is actually variable and unpredictable, with some experiencing long periods of relative stability and some a steady decline, while others rapidly deteriorate (Fig. 18.11.2.6).

There is currently no way to accurately predict the clinical course, although several adverse prognostic factors have been identified (summarized in Table 18.11.2.2). Increasing age has consistently been an adverse prognostic determinant although it is not clear whether disease is, on average more progressive in older people or, as seems more likely, comorbidity (cardiac disease and malignancy) is largely responsible for an adverse outcome. Disease extent and severity at presentation is a crucial consideration. Increased mortality is associated with severe functional impairment, with DLco levels providing the most accurate guidance to likely outcome among lung function tests performed at rest. A composite physiological index, containing DLco, FVC, and FEV_1 levels, has been shown to predict survival more accurately than any single lung function test in isolation. Severe resting hypoxia is indicative of a very poor outcome.

Maximal exercise testing is advocated as a superior prognostic determinant by some authorities but, in reality, there are no convincing data establishing that maximal exercise data are superior to DLco levels in this regard. However, desaturation below 88% during a six-minute walk test has consistently identified IPF patients with a much worse outcome in several series. It is not yet clear whether desaturation during exercise is primarily linked to incipient pulmonary hypertension. The presence of moderate to severe pulmonary hypertension is indicative of a very poor outcome.

HRCT features have also been linked to outcome, with prominent honeycombing associated with a high short-term mortality, although this finding may partially reflect an association between severe honeycombing and extensive disease. Patients with biopsy-proven IPF and HRCT appearances suggestive of NSIP have a better outcome than patients with HRCT appearances typical of IPF.

Smoking status may also be important, based on the observation of a better outcome in IPF in current smokers, than in ex-smokers and lifelong nonsmokers. However, it is not clear whether this provocative observation represents less progressive disease in current smokers, or merely a 'healthy smoker effect' (with smoking cessation linked to more advanced disease).

Observed disease behaviour in patients with IPF is more prognostically accurate than observations made at a single point in time. Serial changes in FVC have consistently predicted mortality more reliably than baseline data: serial DLco trends have been similarly predictive in some but not all reports. Worsening fibrosis on serial imaging or increased dyspnoea both also predict an increased mortality. The distinction between stability and significant decline at 12 months is particularly useful. Once this information is known, in mixed patient populations with UIP or fibrotic NSIP, the histological diagnosis provides no additional prognostic information.

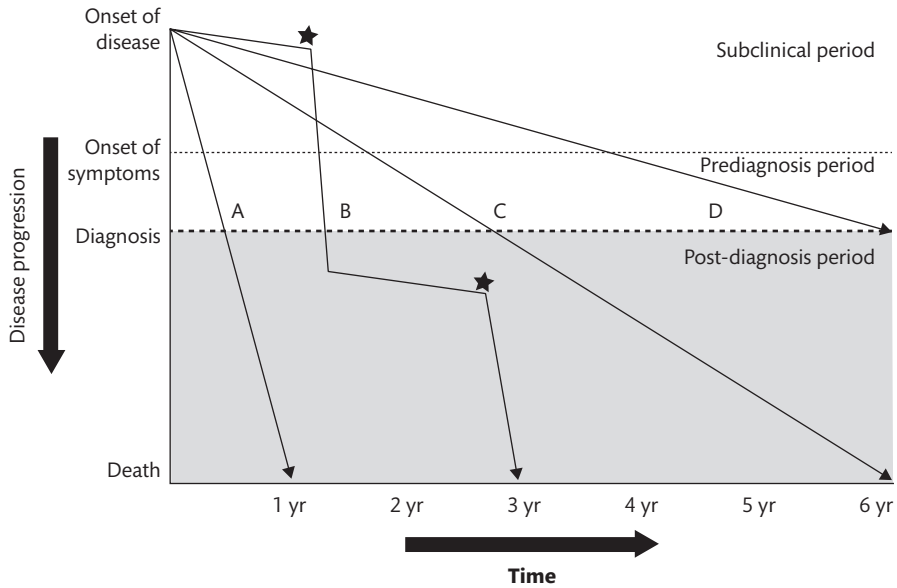

Fig. 18.11.2.6 The potential clinical courses of idiopathic pulmonary fibrosis (IPF). The rate of decline may be rapid (a) or slow (c and d). Acute exacerbations (indicated by the black stars) can affect either course and here creates a mixed picture (curve b).

From Ley B, Collard HR, and King Jr. TE (2011). Clinical Course and Prediction of Survival in Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med*, 183, 431–40.

Table 18.11.2.2 Features associated with a worse outcome in IPF, with evidence graded as possible but uncertain (+/–), definite and moderately useful in routine practice (+), or definite and highly predictive (++).

Features associated with a worse outcome	Grade of evidence
Increasing age	++
Male gender	+/–
Former smoking (versus current smoking)	+/–
High profusion of fibroblastic foci at biopsy	+
Prominent honeycombing on HRCT	++
Presence of pulmonary hypertension	++
Moderate impairment of lung function	+
Resting hypoxia	++
Major desaturation on maximal exercise testing	+
Major desaturation during a six-minute walk test	++
Increasing dyspnoea	+
Serial decline in FVC or DLco	++

Routine monitoring

Lung function tests have traditionally been used to identify treatment responsiveness (in inflammatory disorders) and deterioration (in IPF and other fibrotic disorders). However, measurement variation is a limitation which requires the use of thresholds for 'significant change'. A 10% change from baseline FVC levels, or a 15% change from baseline DLco levels, is required to identify definite regression or progression of disease: the greater measurement variation in DLco may explain the fact that serial FVC trends are more predictive of longer-term outcome than serial DLco trends.

It is also important to recognize that the interpretation of serial lung function must be modified in some contexts. Concurrent emphysema often has a major confounding effect on lung function tests, with spurious preservation of FVC levels, but a disproportionate reduction in DLco (which is reduced in both disorders). In this context, a selective serial decline in DLco levels may be seen, with no change in FVC despite significant progression of disease. A selective reduction in DLco may also be indicative of incipient pulmonary hypertension. Thus, serial lung function trends must be integrated with clinical, HRCT and (when indicated) echocardiographic information. In advanced disease with increasing hypoxia, detailed lung function tests are often impracticable and serial tests tend to be less informative than observations of changes in oxygen saturation (in the steep component of the oxygen dissociation curve).

A marginal reduction in lung function indices (a 5–10% change in FVC levels, a 10–15% change in DLco levels) commonly causes difficulties for clinicians. These changes may indicate true disease progression in some patients, but lie within the measurement variation of lung function tests. Symptomatic change is sometimes a useful guide in this difficult scenario, but is sometimes misleading. Exertional dyspnoea may increase because of disease progression, loss of fitness, comorbidity, or weight gain and myopathy due to corticosteroid therapy. Serial HRCT is sometimes informative, with clear evidence of disease progression in the context of marginal lung function decline. However, serial HRCT should be reserved for situations in which the demonstration of disease progression is likely to influence management: it is difficult to assign significance to minor change on HRCT in the absence of lung function deterioration.

In IPF, the intensity of monitoring is critically dependent upon the therapeutic goal. Regular monitoring at three to four monthly intervals is especially important in patients receiving treatment, especially novel therapies, and when referral for lung transplantation is contemplated. In other cases, in which no change in therapy is contemplated, less frequent monitoring may be appropriate. However, the importance of best supportive care, including the correct use of oxygen in advanced disease, justifies continued monitoring in the long term.

Treatment

The last decade has seen important developments in the treatment of IPF, with several well-conducted negative randomized controlled trials reshaping the therapeutic landscape. Previous therapeutic approaches based around immunosuppression have been shown to be harmful, while compounds with antifibrotic actions have been found to slow decline in lung function.

Immunosuppressive agents

Historically, unsuccessful treatments for IPF were targeted at reducing inflammation, which was incorrectly felt to be the predominant underlying disease process. Large studies have shown no benefits with corticosteroids, and similar results were seen when studying the use of the immunosuppressive agents azathioprine, ciclosporin, and cyclophosphamide. Indeed, far from demonstrating any benefit of immunosuppression with the previous mainstay of treatment, namely a combination of prednisone, azathioprine, and N-acetylcysteine, this has actually proven to be harmful compared to placebo in IPF. Immunomodulatory drugs including IFN-γ, IFN-β, Imatinib, and Etanercept have all been trialled, and despite initial suggestions of benefits in small pilot studies, none have gone on to show any impact on disease progression or survival in larger studies.

Antifibrotic agents

In contrast to negative trials targeting inflammation, two antifibrotic compounds, pirfenidone and nintedanib, have now been proven to slow functional decline in IPF. Pirfenidone, a novel antifibrotic agent with antioxidant and anti-inflammatory effects, became the first drug to be licensed specifically for the treatment of IPF in Europe and the United States. Four randomized controlled trials have now demonstrated that treatment with pirfenidone reduces lung function decline, improves progression-free survival, and reduces all cause mortality at 12 months. It is generally well tolerated, with most side effects related to gastrointestinal symptoms, photosensitivity, and fatigue. These all tend to be mild and easily managed with either life style modifications or dose reduction. Indeed, effective patient education prior to commencement can often avoid significant side effects all together.

Nintedanib is a tyrosine kinase receptor antagonist that inhibits key profibrotic growth factors, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF). Two large phase 3 randomized trials demonstrated that, compared with placebo, nintedanib consistently slowed disease progression by significantly reducing the annual rate of

decline in FVC. There is also a suggestion it may decrease the risk of acute exacerbations of IPF in subjects with more mild disease. It is generally well tolerated, with most side effects gastrointestinal. Up to 60% of subjects in clinical trials experienced diarrhoea, but this was easily managed, and tellingly almost all subjects involved elected to continue with the medication in the following open label phase.

Both pirfenidone and nintedanib slow the decline in FVC in IPF and are now licensed in Europe and the United States for the treatment of mild to moderate IPF (FVC 50–80% predicted). There is no head to head data, and currently little information on the potential for combination therapy. The decision as to which agent to use as first-line treatment is therefore currently based on clinician experience, patient preference, lifestyle, medical history, and concomitant medication. The availability of two agents means that patients intolerant of one can switch, and in the future there may be options for combination or add-on therapy.

Acute exacerbations

In 10–15% of patients each year there is an accelerated deterioration occurring over several weeks and often leading rapidly to a fatal outcome. Pneumonia, heart failure, and pulmonary thromboembolic disease are sometimes the trigger, but the cause for many of these episodes, termed acute exacerbations of IPF, remains poorly understood. Patients typically present with symptoms of worsening dyspnoea, cough, and fever, which are insidious in onset. Investigations focus on excluding known and treatable causes of deterioration, such as infection, heart failure, and pulmonary embolism. After these known causes of deterioration have been excluded and a formal diagnosis of an acute exacerbation of IPF has been made, the treatment remains largely empirical and centred around treating the very same triggers already excluded, with almost all patients initially receiving empirical broad-spectrum antibiotics. If there is no response to antibiotics then patients will subsequently receive trials of high-dose corticosteroids (e.g. 1 g/day methylprednisolone for 3 days), which are either tapered to a lower dose or discontinued based upon clinical response. While these treatments are given, careful attention is paid to optimizing fluid balance status and providing supplementary oxygen therapy. Non-invasive ventilation is sometimes useful, but mechanical ventilation should be avoided due to a uniformly poor outcome.

Transplantation

Single lung transplantation remains the preferred procedure. As in other end-stage lung diseases, a 3-year survival rate of over 50% can be achieved, but a worse outcome is seen in severely deconditioned patients and over the age of 65. The rapidly progressive nature of IPF, compared to other chronic lung diseases, demands the early referral of suitable cases to a transplant centre, ideally before DLco levels fall below 30% of predicted normal.

Supportive therapy

Supportive therapy is central to the management of advanced disease. Supplemental oxygen can be provided in the home through oxygen concentrators, and ambulatory oxygen may be beneficial in improving exercise tolerance. The prompt treatment of complications, including infection and heart failure (sometimes triggered by hypoxia) is also important. In terminal disease, small dosages of opiates alleviate the distressing severe dyspnoea associated with striking reductions in lung compliance.

It is difficult for patients and family members to come to terms with the chronic, relentlessly progressive nature of IPF. The input of medical and nonmedical health-care professionals is indispensable to optimal supportive management: social workers, physiotherapists, and occupational therapists all have important roles to play. Rehabilitation programmes may benefit some patients, although less likely to be useful in preterminal disease.

FURTHER READING

Azuma A, *et al.* (2005). Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*, **171**, 1040–7.

Carrington CB, Gaensler EA, Coutu RE (1978). Natural history and treated course of usual and desquamative interstitial pneumonia. *N Engl J Med*, **298**, 801–9.

Collard HR, King TE Jr, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK (2003). Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*, **168**, 538–42.

Demedts M, *et al.* (2005). High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med*, **353**, 2229–42.

Flaherty KR, *et al.* (2003). Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med*, **168**, 543–8.

Flaherty KR, *et al.* (2003). Radiological versus histological diagnosis in UIP and NSIP: survival implications. *Thorax*, **58**, 143–8.

Flaherty KR, *et al.* (2004). Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? *Am J Respir Crit Care Med*, **170**, 904–10.

Gay SE, *et al.* (1998). Idiopathic pulmonary fibrosis: predicting response to therapy and survival. *Am J Respir Crit Care Med*, **157**, 1063–72.

Heukels P, *et al.* (2019). Inflammation and immunity in IPF pathogenesis and treatment. *Respir Med*, **147**, 79–91.

Hunninghake GW, *et al.* (2001). Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*, **164**, 193–6.

Joint Authors Group (2000). Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med*, **161**, 646–64.

Katzenstein AL, Myers JL (1998). Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification (review). *Am J Respir Crit Care Med*, **157**, 1301–15.

King TE, *et al.* (2014). A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med*, **370**, 2083–92.

King TE, *et al.* (2001). Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med*, **164**, 1171–81.

King TE, *et al.* (2001). Idiopathic pulmonary fibrosis: relationship between histopathologic features and mortality. *Am J Respir Crit Care Med*, **164**, 1025–32.

Lama VN, *et al.* (2003). Prognostic value of desaturation during a six-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med*, **168**, 1084–90.

Latsi PI, *et al.* (2003). Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. *Am J Respir Crit Care Med*, **168**, 531–7.

Maher TM, Strek ME (2019). Antifibrotic therapy for idiopathic pulmonary fibrosis: time to treat. *Respir Res*, **20**(1), 205. doi: 10.1186/s12931-019-1161-4.

Mogulkoc M, *et al.* (2001). Pulmonary function in idiopathic pulmonary fibrosis and referral for lung transplantation. *Am J Respir Crit Care Med*, **164**, 103–8.

Raghu G, *et al.* (2011). An Official ATS/ERS/JRS/ALAT Statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*, **183**, 788–824.
Raghu G, *et al.* (2012). Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med*, **366**, 1968–77.
Raghu G, *et al.* (2015). An official ATS/ERS/JRS/ALAT clinical practice guideline: Treatment of idiopathic pulmonary fibrosis: an update of the 2011 clinical practice guideline. *Am J Respir Crit Care Med*, **192**, e3–19.
Raghu G, *et al.* (2006). Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*, **174**, 810–16.
Raghu G, *et al.* (2018). Diagnosis of idiopathic pulmonary fibrosis: an official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*, **198**, e44–e68.
Richeldi L, *et al.* (2014). Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*, **370**, 2071–82.
Seibold MA, *et al.* (2011). A common MUC5B promoter polymorphism and pulmonary fibrosis. *N Engl J Med*, **364**, 1503–12.
Steele MP, *et al.* (2005). Clinical and pathologic features of familial interstitial pneumonia. *Am J Respir Crit Care Med*, **172**, 1146–52.
Wells AU, *et al.* (2003). Idiopathic pulmonary fibrosis: a composite physiologic index derived from disease extent observed on computed tomography. *Am J Respir Crit Care Med*, **167**, 962–9.
Wolters PJ, *et al.* (2018). Time for a change: is idiopathic pulmonary fibrosis still idiopathic and only fibrotic? *Lancet Respir Med*, **6**, 154–60.

18.11.3 Bronchiolitis obliterans and cryptogenic organizing pneumonia

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ESSENTIALS

The nomenclature of the bronchiolitides is complicated by the interchangeable use of pathological and clinical descriptions and a diversity of classification systems. The four primary histological patterns are (1) organizing pneumonia (also termed proliferative bronchiolitis and bronchiolitis obliterans organizing pneumonia); (2) bronchiolitis obliterans (also termed obliterative bronchiolitis and constrictive bronchiolitis); (3) follicular bronchiolitis; and (4) diffuse panbronchiolitis.

Organizing pneumonia—the most characteristic abnormality is a filling of alveoli with granulation tissue and buds of loose collagen and connective tissue matrix cells with a uniform appearance. Presentation is typically subacute with nonproductive or minimally productive cough, insidious dyspnoea, and systemic symptoms including malaise, fever, or chills, weight loss, and myalgia. Clinical signs are nonspecific. The chest radiograph most commonly shows patchy bilateral peripheral consolidation, which is often basal, and serial radiographs often show migration of infiltrates. High-resolution CT most often shows focal subpleural consolidation, with or without air bronchograms. Corticosteroid therapy is usually effective, with other immunosuppressive agents given to fulminant cases or those that do not respond. Prognosis is usually good, with overall mortality less than 5%.

Bronchiolitis obliterans—results from progressive obliteration of the terminal bronchioles with connective tissue matrix, which is cryptogenic in most cases. The usual presentation is with progressive breathlessness and the most characteristic physical finding is of inspiratory 'squawks', which are reliably indicative of small airway disease. High-resolution CT is often diagnostic, revealing focal areas of decreased attenuation representing regional gas-trapping and associated hypoperfusion, termed 'mosaic attenuation' or 'mosaic perfusion'. The disease is not responsive to treatment, but in cases of diagnostic uncertainty it is reasonable to institute a trial of corticosteroids.

Follicular bronchiolitis—results from polyclonal hyperplasia of lymphoid follicles with formation of germinal centres within the bronchiolar walls. Patients usually present with progressive breathlessness, cough, and symptoms of recurrent respiratory infection. high-resolution CT invariably reveals centrilobular nodules less than 3 mm in diameter. Prognosis is generally good.

Diffuse panbronchiolitis—is characterized by bronchiolocentric inflammation, lymphoid hyperplasia, and an accumulation of interstitial foam cells in the lungs. Patients (most typically Japanese) present with subacute symptoms of cough productive of purulent sputum, dyspnoea, and sometimes weight loss. Survival has been transformed by the use of long-term, low-dose erythromycin therapy.

Introduction

The bronchioles are airways without cartilaginous support and include the terminal bronchioles and the respiratory bronchioles which lead to the alveolar ducts. The nomenclature of the bronchiolitides is complicated by the interchangeable use of pathological and clinical descriptions and a diversity of classification systems. The four primary histological patterns are organizing pneumonia (also termed proliferative bronchiolitis and bronchiolitis obliterans organizing pneumonia), bronchiolitis obliterans (also termed obliterative bronchiolitis and constrictive bronchiolitis), follicular bronchiolitis, and diffuse panbronchiolitis. All four disorders may ablate or obstruct the bronchioles. Organizing pneumonia and bronchiolitis obliterans may be associated with other disease processes (**Table 18.11.3.1**). The terminological similarity between bronchiolitis obliterans and an unrelated acinar disorder, bronchiolitis obliterans organizing pneumonia (BOOP), causes particular confusion as the terms are commonly but incorrectly regarded as synonymous. Because of this widespread confusion bronchiolitis obliterans and BOOP are covered in the remainder of this chapter, as are follicular bronchiolitis and diffuse panbronchiolitis, although BOOP is properly an idiopathic interstitial pneumonia, as recently reclassified by an American Thoracic Society/European Respiratory Society nomenclature committee.

The term 'cryptogenic organizing pneumonia' is preferable to BOOP, but it is likely that both terms will continue to appear in the medical literature for the foreseeable future. Cryptogenic organizing pneumonia/BOOP also involves the bronchioles, but these are not truly obliterated and instead are filled with loose intraluminal

Table 18.11.3.1 Causes of bronchiolitis obliterans and organizing pneumonia

Cause	Bronchiolitis obliterans	Organizing pneumonia
Infection	Viral, mycoplasma	Viral, bacterial, fungal, parasites
Rheumatological disease	Especially rheumatoid arthritis,	Especially dermato/polymyositis, rheumatoid arthritis
Transplantation	Bone marrow, heart/lung, lung	Bone marrow, lung
Drugs	E.g. penicillamine	E.g. amiodarone, sulphasalazine, gold, minocycline
Other	Toxicity from inhaled gases, smoke	Radiotherapy Malignant haematological disorders Immunodeficiency syndromes
Cryptogenic	Cryptogenic	Cryptogenic

fibrous tissue. The clinical presentation, radiological features, physiological features, and responsiveness to treatment differ radically between bronchiolitis obliterans and cryptogenic organizing pneumonia (Table 18.11.3.2). Essentially, bronchiolitis obliterans is an irreversible disorder of small airways whereas cryptogenic organizing pneumonia is a largely reversible disorder of the lung interstitium.

Bronchiolitis obliterans

In common with other forms of bronchiolitis, bronchiolitis obliterans is associated with certain triggers but is cryptogenic in most cases. A viral pathogenesis is often proposed based on the fact that the disease often presents following an apparent respiratory infection, but this is unproven. Occasionally, bronchiolitis obliterans precedes the development of an overt rheumatological disorder.

The disease results from progressive obliteration of the terminal bronchioles with connective tissue matrix. In early reports it was found to progress relentlessly to a fatal outcome. With the advent of CT and the detection of less advanced disease, it is now clear that the natural history is highly variable. Although inexorable progression occurs in some patients, especially those with rheumatological disease, an indolent course is probably more frequent, and some patients who appear to develop the disease after a severe viral insult do not progress even when there is severe airflow obstruction.

Histopathology

The terminal bronchioles are predominantly affected, with variable involvement of the proximal respiratory bronchioles. There is fibrotic obliteration of the airway lumen with an occasional inflammatory component, especially in rheumatological disease (Fig. 18.11.3.1). Diagnostic appearances may be lost in advanced disease as a result of airway occlusion by dense connective tissue matrix, which may render the airways invisible.

Clinical features

The usual presentation is with progressive breathlessness. Wheeze and a sensation of chest tightness are occasionally present as nonspecific consequences (respectively) of constriction of small airways and hyperinflation. Nonproductive cough is frequent, but haemoptysis is not a feature. On examination an expiratory wheeze is occasionally heard, but the more characteristic finding is of inspiratory 'squawks', which are reliably indicative of small airway disease. There may be subtle evidence of rheumatological disease, especially rheumatoid arthritis.

Investigations

Imaging

Chest radiography is normal until disease is advanced. The typical findings are nonspecific, consisting of large lung fields with variable loss of vascular markings (indicative of hyperinflation) but no interstitial abnormalities. High-resolution CT is often diagnostic (Fig. 18.11.3.2). There are focal areas of decreased attenuation representing regional gas-trapping and associated hypoperfusion, termed 'mosaic attenuation' or 'mosaic perfusion'. Such an appearance is occasionally present in pulmonary vascular disease, but mosaicism on CT is enhanced on expiration in bronchiolitis obliterans as density contrasts due to regional gas-trapping are exaggerated. Bronchiectasis and bronchial wall thickening are usually present, hence it is sometimes difficult to distinguish bronchiolitis obliterans from bronchiectasis (in which 'mosaic attenuation' indicative of small airways involvement is generally present).

Lung function tests

Lung function tests show fixed airflow obstruction with an increase in residual volume and total lung capacity. Preservation of the total

Table 18.11.3.2 Contrasting features of bronchiolitis obliterans and organizing pneumonia

	Bronchiolitis obliterans	Organizing pneumonia
Histology	Obliteration of bronchioles	Bronchioles filled with loose fibrous tissue
Chest radiography	Hyperinflation	Consolidation
High-resolution CT	Mosaic attenuation	Consolidation, with occasional reticular elements
Pulmonary function tests	Airflow obstruction	Restrictive defect
Response to therapy	Invariably poor	Good in most cases

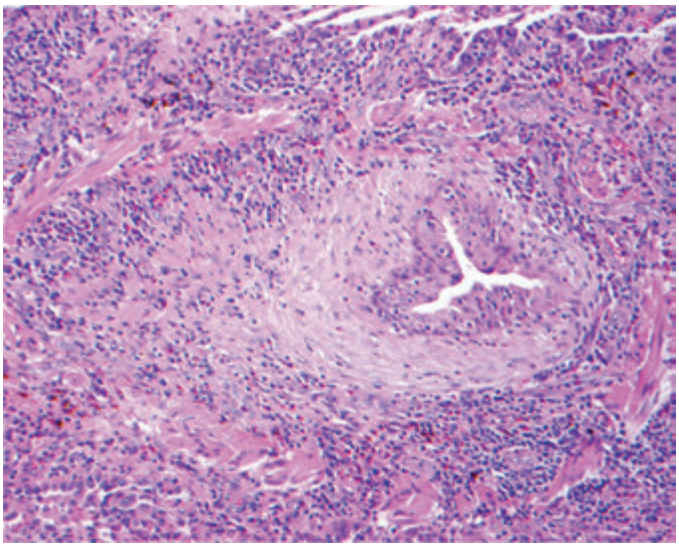

Fig. 18.11.3.1 A case of bronchiolitis obliterans showing virtual occlusion of the bronchiole by a mixture of fibrosis and a chronic inflammatory cell infiltrate that includes scattered eosinophils.

gas transfer for carbon monoxide (D_LCO), except when the forced expiratory volume is 1 s (FEV_1) is less than 1 litre, is a useful ancillary feature distinguishing between intrinsic airway disease and emphysema. The gas transfer index (total gas transfer corrected for alveolar volume) is preserved even when airflow obstruction is severe. Arterial gases at rest remain normal until disease is advanced.

Other investigations

Blood tests show no diagnostic features except when autoantibodies are indicative of unsuspected rheumatological disease. In mild to moderate disease bronchoalveolar lavage shows a characteristic neutrophilia, and absence of eosinophilia may help to distinguish between bronchiolitis obliterans and refractory asthma. Lavage should not be performed in advanced disease as it may cause respiratory decompensation.

Fig. 18.11.3.2 High-resolution CT scan in a patient with severe bronchiolitis obliterans. There is extensive decreased attenuation, indicative of severe gas-trapping, with small areas of increased density representing normal interstitium. There is also severe bronchiectasis, a frequent ancillary finding in advanced bronchiolitis obliterans.

Differential diagnosis

The chronic airflow obstruction of bronchiolitis obliterans is indistinguishable from the chronic airflow obstruction seen in emphysema, bronchiectasis, in some patients with asthma, and in bronchiolitis obliterans complicating other disorders. The diagnosis can generally be made with confidence by reconciling patterns of functional impairment with high-resolution CT appearances. Preserved gas transfer distinguishes intrinsic airways disease from emphysema. The appearances on high-resolution CT are often diagnostic of small airways disease and help exclude emphysema as a cause of airflow obstruction. The auscultatory finding of inspiratory 'squawks' is also strongly indicative of the diagnosis. In early disease the clinical and radiological features may overlap with those of bronchiectasis, but the obstructive defect tends to be much more severe in bronchiolitis obliterans. A surgical biopsy is seldom required to make the diagnosis and is contraindicated in severe airflow obstruction.

Treatment

The disease is not responsive to treatment. In cases of diagnostic uncertainty it is usual to institute a trial of corticosteroids (e.g. prednisolone 40 mg/day for 4 weeks). A significant objective response, based on an improvement in lung function tests, is suggestive of an alternative bronchiolar disorder. Following any response the corticosteroid dosage should be tapered and the minimum maintenance dose should be established. Inhaled steroid therapy and long-acting β_2-adrenoceptor agents such as salmeterol or eformoterol are occasionally efficacious in this context. However, in irreversible disease there is no proven role for long-term corticosteroid or immunosuppressive therapy.

Supportive measures play a crucial role. Patients with bronchiolitis obliterans have difficulty in clearing infective secretions, and in indolent disease prolonged infection may be associated with irreversible worsening of the functional defect. A policy of early antimicrobial therapy for respiratory infection is essential. Enrolment in a pulmonary rehabilitation programme is appropriate in advanced disease. For younger patients with inexorably progressive disease, lung transplantation is the only treatment known to improve life expectancy. There is no evidence that post-transplantation obliterative bronchiolitis, the most common lethal complication of lung transplantation, is more prevalent in patients transplanted for bronchiolitis obliterans.

Organizing pneumonia

Introduction

Organizing pneumonia is a disorder of unknown cause originally described as a clinicopathological entity by Davidson in 1983. Epler and colleagues described a larger series of patients with similar clinical and histological abnormalities which they referred to as 'bronchiolitis obliterans organizing pneumonia' (BOOP) in 1985. Cryptogenic organizing pneumonia is the preferred term because it better describes the clinical and pathological findings, which are

those of an acinar rather than an airway disease, and because the term BOOP is often confused with bronchiolitis obliterans.

Organizing pneumonia can be associated with several other disorders (listed in Table 18.11.3.1) and is then called 'secondary organizing pneumonia'. The clinical features of cryptogenic and secondary disease are very similar, but the distinction is important because the prognosis of secondary disease is often worse.

Histopathology

The most characteristic abnormality is a filling of alveoli with granulation tissue and buds of loose collagen and connective tissue matrix cells with a uniform appearance (Fig. 18.11.3.3). Fibroblasts are embedded in a myxoid matrix containing a variable infiltrate of inflammatory cells forming characteristic polypoid masses known as Masson bodies or 'bourgeons conjunctifs'. The distribution is peribronchial, and airways distal to the terminal bronchiole are also involved. There is variable surrounding chronic inflammation. Supervening interstitial fibrosis, an occasional feature, usually has a pattern of nonspecific interstitial pneumonia.

Clinical features

The incidence and prevalence are unknown. The disease most commonly presents in the sixth and seventh decade, but the age range (20–80 years) is wide. In young adults, underlying rheumatological disease should be suspected. There is no gender predilection. Most patients are non- or ex-smokers.

Presentation is typically subacute with nonproductive or minimally productive cough, insidious dyspnoea, and systemic symptoms including malaise, fever, or chills, weight loss, and myalgia. Wheeze and haemoptysis are rare. Symptoms usually develop over several months and may be preceded by a suspected respiratory tract infection. Rarely, the condition may present as a fulminating illness with acute respiratory failure, and by contrast the disorder can present (5–20% of cases) as an incidental radiological abnormality in an asymptomatic patient, most typically a solitary pulmonary nodule, usually in the upper lobes.

Clinical signs are nonspecific: focal or more widespread crackles are usually, but not always, present. Digital clubbing does not occur. Systemic abnormalities suggestive of rheumatological disease are often subtle and easily overlooked.

Investigations

Imaging

The chest radiograph most commonly shows patchy bilateral peripheral consolidation, which is often basal. Serial radiographs often show migration of infiltrates, a useful diagnostic feature. Extensive reticulonodular abnormalities predominate in occasional cases with extensive supervening interstitial fibrosis. Presentation with a solitary pulmonary nodule is sometimes termed 'unifocal organizing pneumonia'. Pleural abnormalities are rare.

High-resolution CT scans most often show focal subpleural consolidation, with or without air bronchograms (Fig. 18.11.3.4). Ground-glass attenuation is commonly present and sometimes predominates, especially in patients with immune deficiency. Other occasional abnormalities include small (<10 mm) nodules along the bronchovascular bundles, larger nodules, and peripheral reticular abnormalities, denoting supervening fibrosis. The most frequent atypical variant consists of consolidation surrounding bronchovascular bundles, often associated with fibrotic abnormalities and more prevalent in organizing pneumonia complicating polymyositis/dermatomyositis.

Lung function tests

Lung function tests show a restrictive ventilatory defect without coexisting airflow obstruction, and reduced gas transfer. Disproportionate hypoxia may occur due to shunting through dilated vessels within consolidated lung even in apparently limited disease.

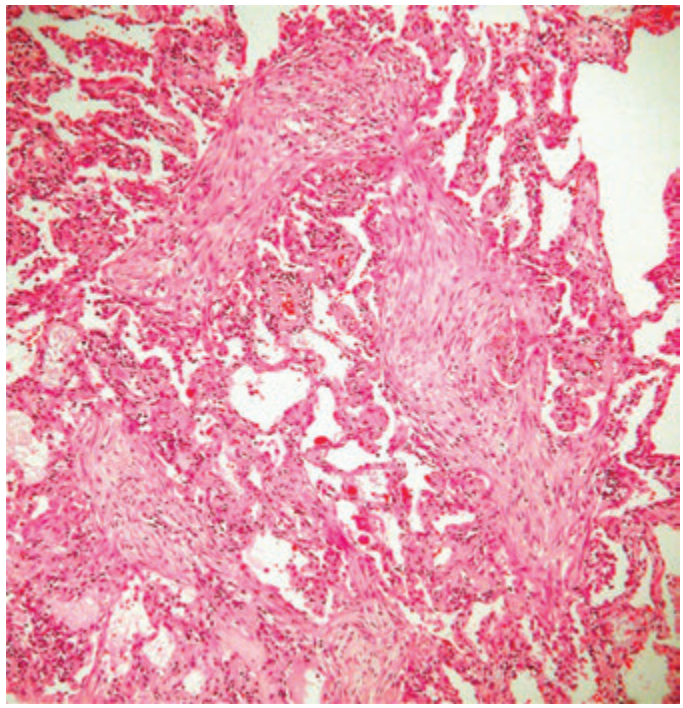

Fig. 18.11.3.3 A case of organizing pneumonia showing intra-alveolar buds of granulation tissue, the typical features of cryptogenic organizing pneumonia when identified in an idiopathic setting.

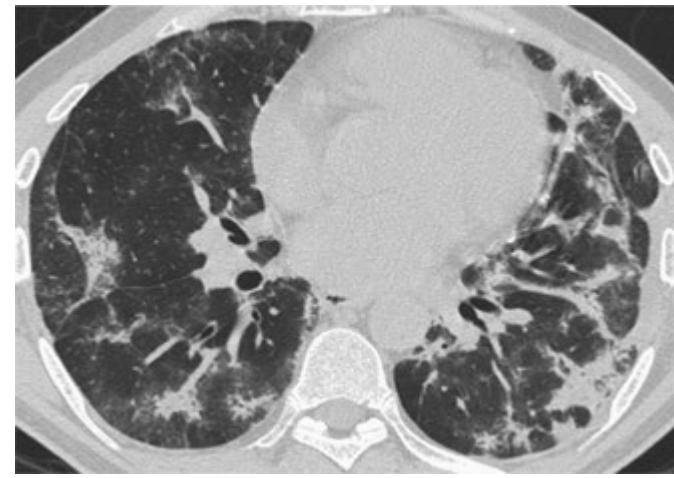

Fig. 18.11.3.4 High-resolution CT scan in a patient with organizing pneumonia. There is bilateral multifocal consolidation which is most prominent subpleurally.

Other tests

Blood tests show nonspecific inflammatory changes, including a markedly raised ESR, raised C-reactive protein, and peripheral blood neutrophilia. Increased autoantibody titres, including antinuclear antibodies, rheumatoid factor, and extractable nuclear antigens, may disclose underlying rheumatological disease that is not clinically overt.

Bronchoalveolar lavage

Abnormalities in bronchoalveolar lavage fluid are nonspecific. However, the usual cell profile of a lymphocytosis (with a low CD4:CD8 ratio) associated with foamy macrophages reduces the likelihood of bacterial infection, vasculitis, or solid cell malignancy. A neutrophilia and/or eosinophilia is not infrequent, and a prominent neutrophilia is reported in patients who progress to extensive fibrosis. Mast cells and plasma cells are occasionally present.

Differential diagnosis

If serial imaging demonstrates that infiltrates are migratory, alternative immunologically mediated abnormalities should be considered, including eosinophilic pneumonia, vasculitis (especially Churg–Strauss vasculitis and Wegener's granulomatosis) and allergic bronchopulmonary aspergillosis. However, fixed consolidation is seen in many patients with cryptogenic organizing pneumonia and in other cases imaging has not been performed before presentation. In this context the differential diagnosis includes infection, alveolar cell carcinoma and other solid malignancies, lymphoma, and alveolar proteinosis. Lung cancer is the usual differential diagnosis in cases that present as a solitary pulmonary mass.

When the clinical and radiological features are typical, the diagnosis may be made if the histological features of organizing pneumonia are evident on a transbronchial biopsy. A bronchoalveolar lavage should also be performed, both to exclude infection and because a compatible cellular profile provides useful diagnostic support, especially when transbronchial biopsies are inconclusive. In some cases, a surgical biopsy is required and this should be of sufficient size to ensure that organizing pneumonia is the main histological finding and not secondary to another pathological process such as infection, vasculitis, or malignancy. It should be stressed that areas of organizing pneumonia may be seen at biopsy in infection, vasculitis, eosinophilic pneumonia, and malignancy. Thus 'sampling error' at transbronchial biopsy occasionally leads to misdiagnosis and the diagnosis should always be reconsidered when the presentation or disease course are atypical. Moreover, histological appearances do not distinguish between cryptogenic disease and secondary organizing pneumonia.

Treatment

There are no controlled studies of treatment, but corticosteroid therapy is usually efficacious, with complete remission in over 60% in published series and a partial response in most of the remaining cases. Response is often rapid, with symptomatic improvement reported within days, although chest radiographic and pulmonary function responses tend to be slower, sometimes requiring up to 3 months of treatment. It is essential that alternative diagnoses be considered in cases that fail to respond.

Until recently initial treatment has generally consisted of oral prednisolone at a dose of 0.75 mg/kg per day, with intravenous methyl prednisolone sometimes used at doses of 500–1000 mg daily for three days in severe disease, followed by prednisolone at 20 mg daily with further reductions tailored according to the clinical course. However, no single recommendation covers all patients and regimens should be adjusted according to initial disease severity and the rapidity and degree of responsiveness. Good response rates were seen in one series with much lower corticosteroid doses (prednisolone 0.75 mg/kg for 4 weeks; 0.5 mg/kg for 4 weeks; 20 mg daily for 4 weeks; 10 mg daily for 6 weeks; 5 mg daily for 6 weeks), relapse rates were not excessive, and the long-term outcome was not adversely affected by rapid withdrawal of prednisolone prior to relapse. Rigorous adherence to traditional regimens in patients with limited disease or a good initial response may therefore result in steroid overtreatment.

Disease which is refractory to corticosteroids may respond to immunosuppressive therapy, such as azathioprine or cyclophosphamide (given orally or intravenously). However, in other cases nonresponsiveness indicates supervening interstitial fibrosis, seen more often in secondary organizing pneumonia, especially that of drug-induced or rheumatological disease. Treatment goals must be adjusted accordingly: once an organizing pneumonia component has been suppressed, prevention of disease progression may become the main therapeutic goal.

Acute fulminating organizing pneumonia rarely presents as the adult respiratory distress syndrome, but with typical organizing pneumonia at biopsy or autopsy. Mechanical ventilation is often required. Such patients are treated with high doses of corticosteroids, with cyclophosphamide most commonly added in those who fail to respond. Rapid progression to death may occur and the overall mortality rate in this group exceeds 50%.

Prognosis

In typical cryptogenic organizing pneumonia the prognosis is usually good, with an overall mortality of less than 5%. Relapses occur in up to 60% of cases as corticosteroids are reduced or stopped, but such relapses respond well to reinstitution of high-dose treatment. A few cases have a poor outcome, with adverse prognostic determinants including a reticular imaging pattern suggestive of pulmonary fibrosis, a prominent neutrophilia, or lack of lymphocytosis on bronchoalveolar lavage, associated connective tissue disease, and histological features of interstitial fibrosis with architectural remodelling of lung parenchyma. Treatment is usually effective in preventing progression of supervening pulmonary fibrosis, but in occasional cases the disease progresses inexorably to a fatal outcome. This is seen more commonly in organizing pneumonia occurring secondary to other disorders, which had a 5-year survival of only 44% in one series.

Unifocal organizing pneumonia presenting as a solitary pulmonary nodule has a uniformly good outcome, with no reported recurrences. The diagnosis is usually made following resection for suspected malignancy.

Follicular bronchiolitis

Follicular bronchiolitis results from polyclonal hyperplasia of lymphoid follicles with formation of germinal centres within the bronchiolar walls. These cause airway obstruction by encroaching

upon or obliterating the bronchiolar lumen. Follicular bronchiolitis may occur as an isolated or primary phenomenon, but more commonly arises secondary to a variety of other conditions such as chronic aspiration or infection (bronchiectasis, cystic fibrosis, lung abscess), tumours, and immune deficiencies including HIV. It is also frequently associated with collagen vascular diseases such as rheumatoid arthritis, systemic sclerosis, and Sjögren's syndrome. When a secondary phenomenon, its clinical presence may be masked by concomitant bronchial or alveolar disease.

Patients usually present with progressive breathlessness, cough, and symptoms of recurrent respiratory infection. They usually have inspiratory crackles, but no finger clubbing. The chest radiograph shows diffuse small nodular or reticulonodular infiltrates but may be normal. High-resolution CT invariably reveals centrilobular nodules less than 3 mm diameter. Peribronchial and subpleural nodules may also occur and patchy, nonsegmental ground-glass opacification is common. Lung function tests may show a restrictive, obstructive, or mixed pattern. Diagnosis of primary follicular bronchiolitis often requires a surgical lung biopsy.

Treatment involves optimum management of any underlying condition. Primary follicular bronchiolitis usually improves with corticosteroids, but other immunosuppressive agents such as azathioprine or methotrexate may be required. The prognosis is generally good, although in younger patients the disease may progress.

Diffuse panbronchiolitis

Diffuse panbronchiolitis is a chronic obstructive pulmonary disease of unknown aetiology that was first described in 1969. The pathological features are a triad of bronchiolocentric inflammation, lymphoid hyperplasia, and an accumulation of interstitial foam cells in the walls of respiratory bronchioles, adjacent alveolar ducts, and alveoli. There may also be luminal collection of neutrophils, but the typical concentric submucosal fibrosis of obliterative bronchiolitis is not a feature.

Diffuse panbronchiolitis is relatively common in Asia, particularly among the Japanese and to a lesser extent Chinese and Koreans, although occasional cases have also been described in Europe and the United States of America. In Japan it is associated with HLA Bw54, an antigen unique to east Asian ethnic groups, while in Korea the association appears to be with HLA A11. This suggests the gene or genes conferring susceptibility lie in the class 1 region between the *HLA-A* and *HLA-B* loci. Any age may be affected, but the mean is around 50 years, and most patients have never smoked. There is a male preponderance of over 2:1. There have been reports of diffuse panbronchiolitis complicating ulcerative colitis and adult T-cell leukaemia.

Patients present with subacute symptoms of cough productive of purulent sputum, dyspnoea, and sometimes weight loss. Up to 75% have chronic sinusitis, which often predates chest symptoms. On auscultation there are widespread coarse crackles and wheeze, but finger clubbing is unusual.

Common features on chest radiography are ill-defined nodules up to 5 mm in diameter, symmetrically distributed, and most prominent in the lung bases. There may also be hyperinflation and in the later stages changes of bronchiectasis become evident. On high-resolution CT centrilobular nodules are evident, often with distal branching structures giving a 'tree in bud' appearance. Thickened, ectatic bronchioles are also seen, and in more advanced disease there is bronchiectasis and air trapping. Pulmonary function tests show an obstructive or mixed picture, and transfer factor is normal or sometimes reduced. Most patients show resting hypoxaemia. Laboratory investigations are nonspecific, but there may be elevated IgA, IgG, and cold agglutinins, and low titres of rheumatoid factor and antinuclear antibodies. In early disease sputum cultures grow *Haemophilus influenzae* or *Streptococcus pneumoniae*, but later *Pseudomonas aeruginosa* predominates. Diagnostic lung biopsy is rarely necessary in countries where the prevalence is high, but may be required elsewhere in the world where the condition is rare.

Without treatment, patients with diffuse panbronchiolitis run a deteriorating course punctuated by episodic superinfections and have 50% mortality at 5 years. However, survival has been transformed by the use of long-term, low-dose erythromycin therapy (400–600 mg daily), which improves lung function and CT appearances and extends 10-year survival to 90%. This improved survival is independent of the presence of *Pseudomonas* infection, suggesting that macrolide therapy works by an anti-inflammatory effect.

FURTHER READING

Cordier J-F (2000). Organising pneumonia. *Thorax*, **55**, 318–28.

du Bois RM, Geddes DM (1991). Obliterative bronchiolitis, cryptogenic organizing pneumonitis and bronchiolitis obliterans organizing pneumonia: three names for two different conditions. *Eur Respir J*, **4**, 774–5.

Epler GR, *et al.* (1985). Bronchiolitis obliterans organizing pneumonia. *N Engl J Med*, **312**, 152–8.

Howling SJ, *et al.* (1999). Follicular bronchiolitis: thin-section CT and histologic findings. *Radiology*, **212**, 637–42.

Kudoh S, *et al.* (1998). Improved survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. *Am J Respir Crit Care Med*, **157**, 1829–32.

Lazor R, *et al.* (2000). Cryptogenic organizing pneumonia: characteristics of relapses in a series of 48 patients. *Am J Respir Crit Care Med*, **162**, 571–7.

Lohr RH, Boland BJ, Douglas WW (1997). Organizing pneumonia. Features and prognosis of cryptogenic, secondary and focal variants. *Arch Intern Med*, **157**, 1323–9.

Muller NL, Miller RR (1995). Diseases of the bronchioles: CT and histopathologic findings. *Radiology*, **196**, 3–12.

Myers JL, Colby TV (1993). Pathologic manifestations of bronchiolitis, constrictive bronchiolitis, cryptogenic organizing pneumonia, and diffuse panbronchiolitis. *Clin Chest Med*, **14**, 611–12.

Ryu JH (2006). Classification and approach to bronchiolar diseases. *Curr Opin Pulmon Dis*, **12**, 145–51.

Verleden SE, Vos R, Verleden GM (2019). Chronic lung allograft dysfunction: light at the end of the tunnel? *Curr Opin Organ Transplant*, **24**, 318–23.

Wells AU (2001). Cryptogenic organizing pneumonia. *Semin Resp Crit Care Med*, **22**, 449–59.

Worthy SA, *et al.* (1997). Mosaic attenuation pattern on thin-section CT scans of the lung: differentiation among infiltrative lung, airway, and vascular diseases as a cause. *Radiology*, **205**, 465–70.

18.11.4 The lung in autoimmune rheumatic disorders

M.A. Kokosi and A.U. Wells

ESSENTIALS

Lung complications occur in all rheumatological disorders, but their frequency and type vary strikingly between different systemic diseases. All components of the lungs can be affected, including the interstitium, airways, pleura, and pulmonary vasculature. Multicompartment involvement of the lung is characteristic. The distinction between subclinical involvement and clinically significant disease is a significant challenge with regard to treatment decisions.

Particular autoimmune disorders

Systemic sclerosis—pulmonary function is abnormal in up to 90% of cases. The most prevalent pattern of lung disease is nonspecific interstitial pneumonia. Both isolated pulmonary vascular disease and secondary pulmonary hypertension occur. Lung cancer is increased in prevalence. Lung and pulmonary vascular disease are now the main cause of morbidity and mortality.

Polymyositis/dermatomyositis—interstitial lung disease, usually with organizing pneumonia or nonspecific interstitial pneumonia, is the commonest pulmonary complication. Aspiration pneumonia is a frequent feature of advanced disease and a common cause of death.

Rheumatoid arthritis—is associated with a wide range of pleuropulmonary complications, including interstitial lung disease (with usual interstitial pneumonia the most frequent pattern, followed by nonspecific interstitial pneumonia), organizing pneumonia, bronchiolitis obliterans, bronchiectasis, pleural effusion, pulmonary vasculitis (rarely), and pulmonary rheumatoid nodules.

Sjögren's syndrome—interstitial lung disease takes the form of fibrotic nonspecific interstitial pneumonia or lymphocytic interstitial pneumonia. Tracheobronchial disease can be in the form of loss of mucus secretion in the trachea (xerotrachea), bronchi and bronchioles, or (less frequently) lymphocytic bronchiolitis.

Systemic lupus erythematosus—clinically significant interstitial lung disease affects about 10% of patients, with nonspecific interstitial pneumonia the usual form. Acute lupus pneumonitis is an uncommon life-threatening disorder. Diffuse alveolar haemorrhage due to capillaritis can occur. The 'shrinking lung syndrome' is thought to be due to respiratory muscle weakness. Pulmonary hypertension is increasingly recognized. Pleural disease is common, affecting 50% of patients at some time.

Pleuroparenchymal fibroelastosis—a newly recognized entity with dense intra-alveolar fibrosis and dense fibrous thickening of the visceral pleura and adjacent lung, which has been described in rheumatic disorders but its prevalence and clinical significance has yet to be defined.

Management

Is treatment required on account of lung disease?—it is critical that high-resolution CT findings and lung function tests are reconciled, with clear definition of all complications and deconstruction of the functional defect. Most clinicians regard DLco levels below 65% of predicted normal as indicative of clinically significant disease. Maximal exercise testing is often useful in marginal cases. Careful monitoring with regular pulmonary function tests should be performed.

Introduction of treatment for lung disease—the threshold for introducing therapy is reduced by three considerations: (1) the risk of progression of lung disease appears to be greatest early in the course of systemic disease; (2) severe functional impairment has consistently been associated with a higher mortality because it is indicative of a previously progressive course and an increased likelihood of future disease progression, also because loss of pulmonary reserve implies that the symptomatic consequences of a further preventable loss of lung function may be substantial; and (3) observed disease progression is a major indication for treatment.

Therapeutic options— immunomodulation remains the cornerstone of therapy. The intensity of the treatment depends on the disease phenotype and behaviour. Treatment decisions are less straightforward in rheumatoid arthritis-associated UIP. The place of antifibrotic drugs such as pirfenidone and nintedanib has yet to be established.

Introduction

Lung complications occur in all rheumatological disorders, but their frequency and type vary strikingly between different systemic diseases. Interstitial lung disease (ILD) and pulmonary vascular disease are now increasingly recognized, although the detection of limited abnormalities poses difficulties for clinicians who must now distinguish between subclinical involvement and clinically significant disease. The presence or absence of exertional dyspnoea is often misleading as musculoskeletal limitation may mask respiratory symptoms or, alternatively, may cause exercise intolerance without lung pathology, due to the increased work associated with inefficient locomotion. Furthermore, ILD precedes the onset of systemic disease in some cases, although typical autoantibody profiles are often diagnostic.

The range of lung histological patterns in rheumatological disease mirrors that seen in the idiopathic interstitial pneumonias, but processes are frequently admixed, with interstitial disease commonly associated with prominent lymphoid follicles (Fig. 18.11.4.1) or pleural thickening (Fig. 18.11.4.2). Nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), and organizing pneumonia are the most frequent findings, with lymphocytic interstitial pneumonia (LIP), acute interstitial pneumonia, and smoking-related disorders (desquamative interstitial pneumonia, respiratory bronchiolitis with associated interstitial lung disease) occurring in occasional cases. However, unlike the idiopathic interstitial pneumonias (see Chapters 18.11.1 and 18.11.2), NSIP is the most frequent pattern, especially in systemic sclerosis and polymyositis/dermatomyositis, partly accounting for the better prognosis consistently reported in lung involvement in rheumatological disorders compared to idiopathic disease in which UIP predominates. The outcome is usually better than in idiopathic fibrotic interstitial pneumonias. Of note, a UIP pattern in connective tissue disorders

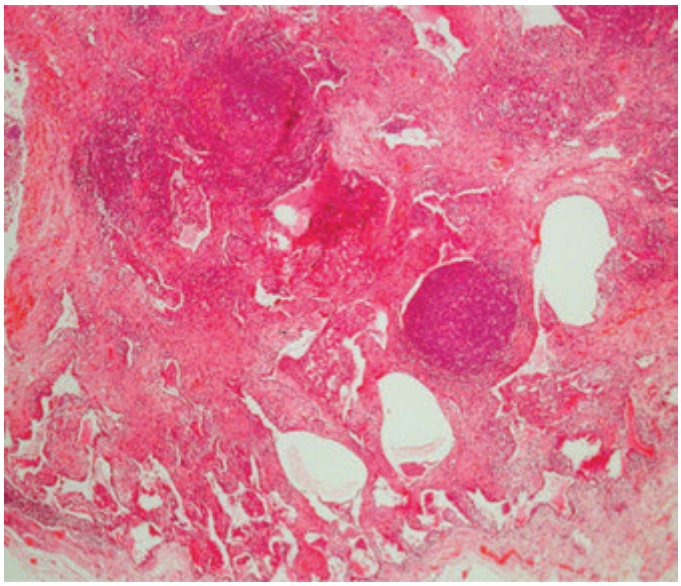

Fig. 18.11.4.1 A case of rheumatoid arthritis involving the lung, with diffuse interstitial fibrosis (fibrotic nonspecific interstitial pneumonia) and prominent lymphoid follicles (reactive germinal centres): an association that is typical of rheumatoid lung.

has been suggested to have a better prognosis than idiopathic pulmonary fibrosis. Rheumatoid arthritis-associated UIP has had a worse prognosis than NSIP in recent series, but overall it seems that UIP does not have a uniformly poor outcome in rheumatoid arthritis.

The clinical features of lung disease in particular rheumatological disorders will now be discussed, followed by consideration of key problems and treatments.

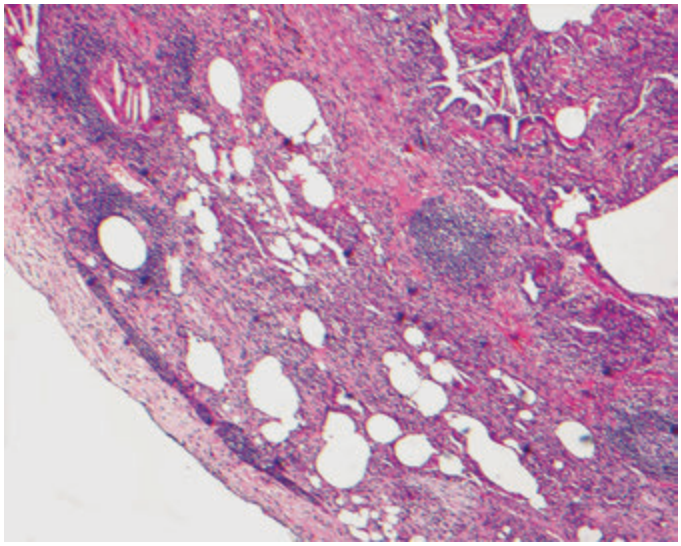

Fig. 18.11.4.2 A case of systemic lupus erythematosis showing thickening of the visceral pleura in association with fibrotic nonspecific interstitial pneumonia.

Systemic sclerosis

The diagnostic criteria for systemic sclerosis are detailed in Chapter 19.11.3. Pulmonary involvement (**Tables 18.11.4.1 and 18.11.4.2**), whether due to lung or pulmonary vascular disease, is now the major source of morbidity and mortality.

Interstitial lung disease

Lung disease (**Table 18.11.4.2**), which consists of NSIP in most cases (**Fig. 18.11.4.3**), occasionally precedes systemic symptoms. Exertional dyspnoea (reported by over 50% of patients at some stage of disease) is the commonest presenting feature. Nonproductive cough is less frequent and pleuritic chest pain is uncommon. Digital clubbing is rare and should raise the suspicion of underlying malignancy. Fine, predominantly basal 'Velcro' crackles are present. Raynaud's phenomenon is a useful clue to the underlying systemic diagnosis, which—in limited disease—is confirmed by capillaroscopy, digital thermography, strongly positive antinuclear antibodies and, in most cases, the presence of the Scl 70 anti-DNA topoisomerase autoantibody. ILD is present on chest imaging at some stage in most patients and may be associated with oesophageal dilatation. Lung function is abnormal in up to 90% of cases, but reduction in carbon monoxide diffusing capacity (D_LCO), the most frequent functional defect, does not in isolation discriminate between interstitial lung disease and pulmonary vasculopathy. Bronchoalveolar lavage is often performed to exclude underlying infection but does not have prognostic value. In NSIP and UIP, granulocytes and lymphocytes are often present in excess, whereas a lymphocytosis is the rule in organizing pneumonia, with a granulocytosis usually indicative of supervening fibrosis.

Pulmonary vascular disease

Both isolated pulmonary vascular disease and secondary pulmonary hypertension (complicating extensive interstitial lung disease) occur. Isolated pulmonary vascular disease takes the form of concentric fibrosis, with ablation of arteriolar intima and media but no vasculitic element. This mainly complicates limited systemic sclerosis (including the CREST syndrome—calcinosis, Raynaud's phenomenon, oesophageal dysmotility, sclerodactyly, teleangiectasia) and is typically associated with the anticentromere autoantibody. There is usually no evidence of interstitial lung disease on chest radiography, high-resolution CT, or bronchoalveolar lavage, and lung function tests generally show an isolated fall in D_LCO or a disproportionate reduction in D_LCO in patients with coexisting lung involvement. Doppler echocardiography is often diagnostic and is widely used as a screening test, but is insensitive in early disease because of the large reserve in the pulmonary vascular bed. Isolated pulmonary vascular disease is a common cause of mortality and is partly responsible for the very poor prognosis associated with marked reduction in D_LCO in clinical series.

Other pulmonary complications

Lung cancer is increased in prevalence, even in nonsmokers, with adenocarcinoma more frequent than other histological subtypes. Extrapulmonic restriction due to severe cutaneous involvement is an

Table 18.11.4.1 Pulmonary complications in autoimmune rheumatic disorders, with the range in prevalence, from rare (±) to frequent (++), indicated semiquantitatively (?, unknown prevalence)

	Rheumatoid arthritis	Systemic sclerosis	Polymyositis/ dermatomyositis	Systemic lupus erythematosus	Sjögren's syndrome
Constrictive (obliterative) bronchiolitis	+	±	±	+	+
Bronchiectasis	++	±	±	+	+
Pleural disease	++	±	±	++	±
Respiratory muscle weakness	?	?	++	±	?
Pulmonary hypertension	±	++	±	++	±
Diffuse alveolar haemorrhage	±	?	±	+	?

extremely rare finding. Pleural disease and organizing pneumonia have been reported occasionally. Despite the fact that oesophageal dysfunction is common, aspiration pneumonia seldom occurs.

Polymyositis/dermatomyositis

Diagnostic criteria for polymyositis and dermatomyositis are described in Chapter 19.11.5. Pulmonary disease (Table 18.11.4.1), occurring in up to 60% of patients, is the most frequent cause of death. Pleural and airways involvement are rare.

Interstitial lung disease

Interstitial lung disease is the commonest pulmonary complication of polymyositis/dermatomyositis (Table 18.11.4.2). Although the presentation is usually with organizing pneumonia or NSIP, a rapidly progressive form of acute pneumonitis occurs more frequently than in other rheumatological disorders. Lung disease (usually organizing pneumonia) precedes systemic disease in up to one-third of patients. Acute exacerbation can occur and manifests as acute or subacute diffuse alveolar damage. Pulmonary capillaritis resulting in haemoptysis has occasionally been reported.

Exertional dyspnoea is a common presenting symptom and orthopnoea is occasionally prominent, especially when myopathy is severe. Cough is a frequent feature, especially in organizing pneumonia, but is seldom severe. Haemoptysis and pleuritic chest pain are rare. In fibrotic disease, fine basal 'Velcro' crackles are usual, and these are variably present in organizing pneumonia.

Organizing pneumonia is often obvious on chest radiography, but high-resolution CT is usually diagnostic and demonstrates the characteristic combination of patchy consolidation and fibrotic disease with bronchocentric and lower zone distribution (the classic form of admixed NSIP and organizing pneumonia). Lung function tests usually show a restrictive ventilatory defect with a reduction in D_LCO. When reduced lung volumes are associated with preservation of D_LCO and an increase in the gas transfer index (*K*CO), extrapulmonic restriction due to respiratory muscle weakness should be suspected. Bronchoalveolar lavage is useful in discriminating between infection and autoimmune organizing pneumonia, especially when immunosuppressive therapy has previously been instituted for systemic disease, but has little value in prognostic evaluation. Autoantibodies to aminoacyl-tRNA synthetase, especially Jo-1 (antihistidyl tRNA synthetase) are often present when prominent inflammatory myopathy coexists with diffuse lung disease, but are found in less than 5% of patients without diffuse lung disease.

Other pulmonary manifestations

Aspiration pneumonia, a very frequent feature of advanced disease and a common cause of death, should also be considered in earlier disease if there is upper airway/pharyngeal or oesophageal muscle weakness, especially when the dependent lung regions are selectively involved. Respiratory muscle weakness, occurring in up to 5% of patients, may occasionally lead to hypercapnic respiratory failure but requires muscle function testing for confirmation in milder cases. Mild pulmonary hypertension is increasingly recognized, although the exact prevalence is uncertain, but vascular involvement is generally self-limited. Lung cancer has increased incidence in polymyositis/dermatomyositis, which in these cases might represent a paraneoplastic feature.

Table 18.11.4.2 Histological patterns of interstitial lung diseases in autoimmune rheumatic disorders, with the range in prevalence, from rare (±) to frequent (++), indicated semiquantitatively (?, unknown prevalence)

Lung pattern	Rheumatoid arthritis	Systemic sclerosis	Polymyositis/ dermatomyositis	Systemic lupus erythematosus	Sjögren's syndrome
Usual interstitial pneumonia	++	+	+	+	±
Nonspecific interstitial pneumonia	++	+++	++	++	++
Organizing pneumonia	+	±	++	±	±
Lymphocytic interstitial pneumonia	±	±	±	±	++
Pleuroparenchymal fibroelastosis	?	?	?	?	?
Desquamative interstitial pneumonia and/or RB-ILD	±	±	±	±	±
Diffuse alveolar damage	+	±	+	+	±

Fig. 18.11.4.3 High-resolution CT scan in a patient with systemic sclerosis. There is prominent ground-glass attenuation, admixed with fine reticular abnormalities: these appearances are typical of nonspecific interstitial pneumonia.

Rheumatoid arthritis

Diagnostic criteria for rheumatoid arthritis are detailed in Chapter 19.5. Pleuropulmonary complications (Table 18.11.4.1) are more variable than in other rheumatological disorders.

Interstitial lung disease

Interstitial lung disease (Table 18.11.4.2) has a male predominance (male:female 3:1) and is associated with high titres of rheumatoid factor, the presence of rheumatoid nodules, a history of smoking, and HLA B8 and HLA Dw3 positivity. UIP is the most prevalent histologic pattern in rheumatoid arthritis, followed by NSIP. Interstitial lung disease precedes the onset of systemic disease in about 15% of cases.

Exertional dyspnoea is the most frequent presenting symptom, with nonproductive cough also common, especially in patients with sicca symptoms. Bilateral, predominantly basal 'Velcro' crackles are usual and digital clubbing is more prevalent than in other rheumatological diseases.

Acute exacerbations of underlying interstitial lung disease can occur and have poor prognosis, similar to that of acute exacerbations in idiopathic pulmonary fibrosis. Drug reactions and infections should be considered in the case of acute deterioration.

Radiologically overt interstitial lung disease, usually with a basal predominance, was present in less than 5% of cases in three large chest radiographic series. High-resolution CT often shows limited interstitial abnormalities when chest radiographs are normal, although the significance of 'subclinical' disease has yet to be ascertained. In established disease, a restrictive ventilatory defect is associated with reduced D_LCO levels, but an isolated reduction of D_LCO is seen in up to 40% of unselected rheumatoid arthritis patients. As in other rheumatological disorders, bronchoalveolar lavage may be very useful when opportunistic infection is suspected, but it has limited routine value when disease is overtly fibrotic.

Organizing pneumonia

Organizing pneumonia more commonly mimics infectious pneumonia in rheumatoid arthritis than in polymyositis/dermatomyositis. Cough and exertional dyspnoea are commonly accompanied by fever and weight loss. There is multifocal consolidation on chest radiography and high-resolution CT. Lung function tests show a restrictive defect and reduced D_LCO, often associated with disproportionate hypoxia due to shunting through consolidated lung. A lymphocytosis is usual on bronchoalveolar lavage, with a granulocytosis usually indicative of underlying fibrotic disease. Organizing pneumonia responds well to corticosteroid therapy in most cases.

Bronchiolitis obliterans

This rare but often lethal bronchiolar disorder usually presents with exertional dyspnoea, often with a component of wheeze and nonproductive cough. The breath sounds are usually quiet, with inspiratory 'squawks' a very specific sign of small-airways disease.

An association with the use of penicillamine was postulated in the first descriptions of obliterative bronchiolitis 20 to 30 years ago. Based on subsequent case reports and small series this is probably a true association, but it should be stressed that more cases of obliterative bronchiolitis are seen in patients with rheumatoid arthritis who have not used penicillamine than in those who have.

The chest radiograph is normal or shows hyperinflation. High-resolution CT shows a 'mosaic' pattern which is more obvious on expiratory images and represents regional gas trapping. In most cases the lung function defect is obstructive, although there is occasionally a mixed obstructive/restrictive pattern. Measures of gas transfer (D_LCO and KCO) are preserved provided the forced expiratory volume in 1 s (FEV_1) exceeds 1 litre. Preservation of gas transfer is especially useful in discriminating between obliterative bronchiolitis and emphysema, in which both D_LCO and KCO are significantly reduced. Bronchiolitis obliterans is characterized histologically by fibrous destruction and ablation of the terminal bronchiolar wall by granulation tissue.

Although a fatal outcome was almost invariable in early reports, the increasing use of high-resolution CT has disclosed many patients with milder disease in whom the course is often indolent.

Bronchiectasis

Bronchiectasis is more prevalent in rheumatoid arthritis than in other rheumatological diseases. From a definitive literature review of 289 rheumatoid arthritis patients with associated bronchiectasis reported since 1928, it is clear that the condition precedes the onset of systemic disease in some cases. Before the routine use of high-resolution CT bronchiectasis was generally diagnosed in patients presenting with chronic purulent sputum production. However, it is increasingly apparent that asymptomatic ('dry') bronchiectasis is extremely common, being present on high-resolution CT in 30% of 50 rheumatoid arthritis patients with normal chest radiographs on prospective evaluation. The high-resolution CT overlap between bronchiectasis and obliterative bronchiolitis should be stressed. Bronchiectasis and a 'mosaic' pattern may coexist in both disorders, and bronchiectasis is often present in rheumatoid arthritis patients with interstitial lung disease.

Pleural disease

Pleural involvement is present at autopsy in about 50% of cases, but only 20% of patients experience pleuritic pain at some stage and most pleural effusions are found incidentally on chest radiography. Clinically overt pleural effusions occur in less than 5% of patients, usually in males, but evidence of pre-existing pleural disease is found on screening chest radiography in up to 20%. Pleural disease has been linked to the presence of rheumatoid nodules but not to more severe systemic disease.

Symptoms are confined to a minority of cases and generally consist of pleuritic pain and prominent fever, often necessitating the exclusion of empyema. Effusions may occasionally develop acutely in association with pericarditis or exacerbations of arthritis. Dyspnoea may result from pulmonary compression when effusions are large, especially when there is underlying interstitial lung disease. The fluid is exudative, with a low glucose level, a low pH, and usually a predominant lymphocytosis. The most frequent histological finding is replacement of the normal mesothelial cell covering by a pseudostratified layer of epithelioid cells, with focal multinucleated giant cells and regular small papillae containing branching capillaries, but no necrosis or granulomata. These findings are pathognomonic for rheumatoid pleuritis when present, but histological appearances are often nonspecific.

Some cases respond well to corticosteroid therapy, but more often remission is at best partial.

Pulmonary vasculitis

Pulmonary vasculitis is a surprisingly uncommon complication of rheumatoid arthritis given the relatively high prevalence of systemic vasculitis in the disease. However, it is likely that pulmonary vasculitis is not detected in many cases as the diagnosis is often elusive. Diffuse alveolar haemorrhage has been reported in a handful of cases.

Pulmonary rheumatoid nodules

These are present on chest radiography in less than 1% of patients and are usually associated with subcutaneous rheumatoid nodules. Caplan's syndrome consists of the association of pulmonary nodules, especially cavitating nodules, with coal miner's pneumoconiosis. Single nodules in cigarette smokers often require histological confirmation of the diagnosis (by means of percutaneous needle or surgical biopsy) as malignancy cannot be excluded noninvasively. Nodules may fluctuate in size, waxing and waning with variations in underlying rheumatoid activity, and can reach 5–10 cm in diameter. Usually nodules are asymptomatic and found incidentally on chest radiography, but they often cavitate (50%) and can rupture, giving rise to haemoptysis, pneumothorax, or bronchopleural fistula. Multiple nodules occasionally occur, with respiratory failure a reported complication of intense nodular infiltration.

Other pulmonary manifestations

Nonproductive cough due to secondary Sjögren's syndrome is not uncommon in rheumatoid arthritis and may result from either impaction of viscid secretions within small airways or from a lymphocytic bronchiolitis, often associated with enlargement of lymphoid follicles. Full-blown follicular bronchiolitis is a rare disorder (see Chapter 18.11.3), in which reticulonodular chest radiographic appearances are often suggestive of interstitial lung disease and lung function tests may be restrictive or obstructive. Unlike obliterative bronchiolitis, follicular bronchiolitis often responds to corticosteroid therapy. Lymphocytic interstitial pneumonia is a rare benign lymphoproliferative disorder which may be limited or extensive, presents as an interstitial lung disease, and is variably responsive to corticosteroids. Desquamative interstitial pneumonia is rare.

Lower respiratory tract infection is increased in frequency in rheumatoid arthritis, especially in advanced disease. Bronchopneumonia is a common terminal event, accounting for 15 to 20% of deaths.

Pulmonary hypertension occurs in up to 20% of patients with rheumatoid arthritis and is usually mild and secondary to interstitial lung disease, but occasionally it can result from a primary vasculopathy.

Sjögren's syndrome

The diagnostic criteria for Sjögren's syndrome are detailed in Chapter 19.11.4. There is evidence of pulmonary abnormalities (Table 18.11.4.1) in about one-quarter of cases, but disease is usually self-limited and seldom progresses to severe disability or death.

Interstitial lung disease

Parenchymal disease (Table 18.11.4.2), once thought to consist exclusively of lymphocytic infiltration (lymphocytic interstitial pneumonia) based on historical series, occurs in up to 10% of patients. However, it is increasingly recognized that clinically significant disease more often consists of fibrotic NSIP (with UIP very seldom reported).

Interstitial lung disease is often asymptomatic but may declare itself with cough or exertional dyspnoea. The findings are nonspecific, consisting of crackles on auscultation, reticular or reticulonodular abnormalities on chest radiography, and a restrictive ventilatory defect associated with a reduction in DLco. High-resolution CT discriminates usefully between these processes. Fibrotic NSIP is characterized by reticular abnormalities and traction bronchiectasis and in some occasions ground glass. LIP is characterized by ground glass and cystic changes. LIP can evolve to pulmonary lymphoma occasionally. Extrapulmonary lymphoma is also increased in prevalence in Sjögren's syndrome and is probably as frequent as pulmonary lymphoma. Lymphoma often mimics organizing pneumonia, which has occasionally been reported in Sjögren's syndrome.

Tracheobronchial disease

Tracheobronchial disease may take two forms. The more frequent disorder consists of loss of mucus secretion in the trachea (xerotrachea), bronchi, and bronchioles. Xerotrachea occurs in up to 25% of patients with primary Sjögren's syndrome in older series, but may be less prevalent with the increasing recognition of milder variants of the syndrome. The histological picture consists of atrophy of tracheobronchial mucous glands, with or without a lymphoplasmacytic infiltrate. Less frequently, airway disease is due to a lymphocytic bronchiolitis, and occasionally there is considerable enlargement of lymphoid follicles (follicular bronchiolitis). Both xerotrachea and lymphocytic bronchiolitis present with an unremitting dry cough. Endobronchial inflammation is often

obvious at bronchoscopy and there is an increased prevalence of bronchial hyperresponsiveness, reported in 40 to 60% of patients with Sjögren's syndrome, and studies of airflow at low lung volumes in unselected patients disclose a high prevalence of small-airway disease. The increased viscidity of secretions results in a high prevalence of secondary infection and in some patients the predominant feature is recurrent episodes of bronchopneumonia. Lymphocytic bronchiolitis usually responds to oral or inhaled corticosteroid therapy, but the increased risk of oral candidiasis in Sjögren's syndrome needs to be kept in mind. Xerotrachea responds variably to nebulized saline.

Systemic lupus erythematosus

The diagnostic criteria for systemic lupus erythematosus (SLE) are detailed in Chapter 19.11.2. Pleuropulmonary manifestations are listed in Table 18.11.4.1.

Diffuse lung disease

Although limited interstitial fibrosis is found at autopsy in up to 70% of patients, it is likely that this represents post-inflammatory sequelae in most cases. Clinically significant interstitial lung disease is present in less than 5% of patients at the onset of systemic disease, and develops in a further 5% during follow-up. The clinical presentation closely resembles that of interstitial lung disease in other rheumatological disorders and typically includes dyspnoea, cough, predominantly basal crackles and a restrictive lung function defect or isolated reduction in D_LCO, and predominantly basal reticulonodular abnormalities on chest radiography. There are no definitive reports of typical high-resolution CT appearances, although there is a high prevalence of limited subclinical interstitial abnormalities. The most common histological pattern is NSIP, although UIP has also been reported (Fig. 18.11.4.2).

Acute lupus pneumonitis is an uncommon life-threatening disorder, seen in less than 2% of patients, but with a mortality rate despite treatment of up to 50% once respiratory failure has developed. It may resemble organizing pneumonia, which is very infrequent in SLE. It is believed by some that acute lupus pneumonitis represents an aberrant immunological response to infection, facilitated by the intrinsic immune defect of the systemic disease.

Extrapulmonary restriction

Extrapulmonary restriction in SLE takes the form of the 'shrinking lung syndrome', consisting of a marked reduction in lung volume on chest radiography in association with a restrictive functional defect, preservation of D_LCO, and a marked increase in KCO. The lung interstitium is normal and the disorder is thought to represent respiratory muscle weakness, especially diaphragmatic weakness. The syndrome is usually self-limited, although producing severe exercise limitation in more advanced cases. Improvements have been reported with corticosteroid or immunosuppressive therapy, but these appear to be unpredictable and there is no other efficacious treatment.

Diffuse alveolar haemorrhage

Diffuse alveolar haemorrhage due to capillaritis occurs more frequently than in other rheumatological conditions but is still rare in SLE. It occurs in 1.5% of cases, and is the initial presentation in 10–20% of these. Typically, patients present with subacute or acute dyspnoea and extensive infiltrates on chest radiography. Haemoptysis is occasionally torrential but is more often minimal or absent, even when there is extensive intra-alveolar haemorrhage. The presentation is similar to those of acute lupus pneumonitis and opportunistic infection, especially in the absence of haemoptysis. The diagnosis is best made by bronchoalveolar lavage, when increasingly heavy blood-staining is typical as the distal airways are lavaged in cases without overt endobronchial haemorrhage. Diffuse alveolar haemorrhage is life-threatening with a mortality of up to 50% in patients with respiratory failure. There are no definitive treatment data, but empirical treatments have included intravenous corticosteroid therapy, intravenous cyclophosphamide, rituximab, and plasmapheresis.

Pulmonary hypertension

Pulmonary hypertension, once regarded as rare, is encountered with increasing frequency. In early reports, largely containing patients with severe disease, the 2-year mortality approached 50%. However, with the increasing use of echocardiography, subclinical pulmonary vascular abnormalities are detected in 10% of patients. In some cases associated with Raynaud's phenomenon it appears that vasoconstriction with secondary irreversible damage is the dominant pathophysiological mechanism. In other cases vasculitis predominates, and this may respond strikingly to corticosteroid therapy or intravenous cyclophosphamide, even in advanced disease. Thromboembolism or microthrombosis in small intrapulmonary arterioles also occur in many cases, especially when antiphospholipid antibodies are present. It is often impossible to determine which mechanism predominates as surgical biopsy is contraindicated by severe pulmonary hypertension. Treatment is empirical, consisting of immunosuppression, anticoagulation, and a variety of vasodilator agents.

Pleural disease

Pleural disease is common in SLE. There is clinical or radiographic evidence of pleural involvement in 20% of patients at the onset of systemic disease, and at least 50% have overt pleural involvement at some time. Pleural disease is often detected on incidental chest radiography in asymptomatic patients, but in other cases pleuritic pain is recurrent or intractable. The pleural fluid is usually serosanguinous and exudative, with a high neutrophil content in patients with pleurisy, but a predominant lymphocytosis is the rule in chronic disease and in some cases, effusions are haemorrhagic. Corticosteroid therapy is usually much more efficacious than in rheumatoid arthritis.

Relapsing polychondritis

Relapsing polychondritis is described in Chapter 19.11.9. Respiratory involvement accounts for about 10% of deaths and takes the form of obstruction of the glottis, trachea, and bronchi, leading to airway stricture, collapse, and distal infection. Pulmonary vasculitis is common but often subclinical, and pulmonary hypertension is rare. Parenchymal disease seldom occurs in isolated relapsing polychondritis, but many other autoimmune conditions, including

most rheumatological disorders, are associated with relapsing polychondritis and may be complicated by interstitial lung disease.

Lung function tests typically show severe airflow obstruction due to airway collapse, with reduced maximal inspiratory and expiratory flow representing extrathoracic and intrathoracic airway involvement, respectively. Airway abnormalities are prominent on chest radiography, with bronchiectasis and bronchial wall thickening evident on high-resolution CT. Bronchoscopy has been reported to trigger fatal airway obstruction and should be undertaken with caution. The diagnosis may be made using dynamic CT scanning showing collapse of the larger airways on inspiratory manoeuvres. However, definitive diagnosis requires biopsy, which often shows characteristic features in extrapulmonary cartilaginous areas.

Immunosuppression is sometimes effective in preventing disease progression, and mechanical stenting may be life-saving in advanced destructive disease. Traditionally, flares of relapsing polychondritis have been treated with corticosteroid therapy or immunosuppressants, but—based on recent accumulated experience—anti-TNF agents are increasingly used, and they are advocated by some as first-line treatment.

Ankylosing spondylitis

Ankylosing spondylitis is described in Chapter 19.6. Interstitial lung disease is a rare complication, identified on chest radiography in less than 2% of cases, although subclinical interstitial abnormalities are highly prevalent on high-resolution CT, including fibrotic abnormalities and paraseptal emphysema. Fibrobullous lung disease is largely or entirely confined to the upper zones and is usually symmetrical. Fibrotic abnormalities may be more extensive in occasional patients with severe long-standing spinal disease.

Interstitial lung disease does not respond to corticosteroid therapy and immunosuppressive therapy has no recognized role and may predispose to chronic infection. Cavities tend to develop within distorted fibrotic apical tissue and are often colonized by mycobacteria or fungi, especially *Aspergillus fumigatus*. Life-threatening haemoptysis is an occasional complication of intracavitary mycetoma formation. Bronchial artery embolization is sometimes effective, but surgical resection of a mycetoma is generally held to be contraindicated and carries a high mortality due to postoperative bronchopleural fistula formation and empyema.

Extrapulmonary restriction is more frequent than interstitial lung disease and results from immobilization of the chest wall due to fusion of the costovertebral joints. This complication is often asymptomatic and the lung function defect is mild, perhaps because the diaphragm is able to compensate for chest-wall immobility. Exercise tolerance is seldom impaired, provided that an active lifestyle is maintained. Chest-wall fixation increases in prevalence and severity in long-standing disease and does not respond to anti-inflammatory treatment. Management is confined to spinal extension exercises and the maintenance of general fitness with exercise programmes.

Mixed connective tissue disease

In this syndrome there are variable features of SLE, systemic sclerosis, and polymyositis/dermatomyositis in association with high titres of autoantibody directed against the extractable nuclear antigen U1-RNP. However, the diagnosis is often elusive because clinical features evolve as disease progresses and individual criteria may be ephemeral. Pulmonary involvement encompasses the full spectrum of disease seen in systemic sclerosis, polymyositis/dermatomyositis, and SLE, the three most frequent disorders being pleural effusions, interstitial lung disease, and pulmonary hypertension.

Pleuritic pain is reported by up to 40% of patients, but effusions are typically small and generally remit spontaneously. Interstitial lung disease is even more prevalent and usually mimics the interstitial fibrosis of systemic sclerosis: organizing pneumonia is surprisingly infrequent and, when present, is generally self-limited. Pulmonary vascular disease is well recognized and is occasionally fatal: reported mechanisms include, most commonly, vasoconstriction in association with arteriolar obliteration, as in systemic sclerosis, but also pulmonary vasculitis and pulmonary thromboembolism.

Other rare pulmonary complications are those of the dominant rheumatological picture and include respiratory muscle weakness, severe diffuse alveolar haemorrhage, aspiration pneumonia due to pharyngeal dysfunction, and opportunistic infection in patients receiving immunosuppressive therapy. The investigation and management of pulmonary complications is as for the individual rheumatological diseases. Long-term outcome has not been quantified with any precision.

Undifferentiated connective tissue disease

Many patients with an idiopathic interstitial pneumonia have clinical features that suggest an underlying autoimmune process but do not meet established criteria for a connective tissue disease. Researchers have proposed differing criteria and terms to describe these patients, and lack of consensus recently led to the proposal of interstitial pneumonitis with autoimmune features (IPAF). The classification criteria are organized around the presence of a combination of features from three domains: a clinical domain consisting of specific extrathoracic features, a serologic domain consisting of specific autoantibodies, and a morphologic domain consisting of specific chest imaging, histopathologic, or pulmonary physiologic features. The definition of IPAF requires that the patient fulfils two of the three domains. The clinical significance of IPAF needs to be further studied.

Key clinical problems in interstitial lung disease in patients with rheumatological disorders

Detection of disease

The reported prevalence of interstitial lung disease is critically dependent on which diagnostic modality is used. Rheumatoid arthritis patients without overt lung involvement were found to have interstitial fibrosis in almost one-half of cases in an early biopsy study, yet abnormalities are present on chest radiography in less than 5%. Chest radiography is now known to be insensitive and symptoms are often misleading.

There is an increasing tendency to screen patients with rheumatoid arthritis, systemic sclerosis, and polymyositis/dermatomyositis

for interstitial lung disease as lung involvement is most prevalent in these disorders. However, lung function tests are often difficult to interpret, as minor abnormalities, especially isolated reductions in *DLco*, occur in most patients. Even normal lung function tests may be misleading: the normal range is wide and may conceal substantial loss of lung function in some cases. Moreover, pulmonary function variables are affected by several pulmonary and extrapulmonary comorbidities, including airway disease (such as obliterative bronchiolitis or bronchiectasis), concurrent smoking-related emphysema, pulmonary vascular disease, pleural disease, respiratory muscle weakness, and other forms of extrapulmonary limitation.

Bronchoalveolar lavage was once widely advocated as a means of detecting underlying alveolitis, but abnormalities are present in most patients with systemic sclerosis, ankylosing spondylitis, and Sjögren's syndrome, and are probably equally prevalent in the other rheumatological diseases. Subclinical alveolitis has never been shown to evolve into clinically significant interstitial lung disease and hence this use of bronchoalveolar lavage is largely discredited. High-resolution CT is the most sensitive and reliable means of detecting interstitial lung disease but should probably be reserved for patients with symptoms, chest radiographic abnormalities, lung function impairment, or high-risk patients (e.g. patients with systematic sclerosis (SSc) who are positive for anti-topoisomerase or anti-RNA polymerase III antibodies).

Determination of clinically significant disease

The advent of high-resolution CT has undoubtedly helped clinicians greatly in identifying interstitial lung disease, but has led to a separate problem: the identification of limited subclinical abnormalities. Severe interstitial fibrosis is rare in Sjögren's syndrome, SLE, and ankylosing spondylitis, but high-resolution CT abnormalities are present in many patients. In unselected patients with rheumatoid arthritis, interstitial lung disease is evident in 25% of cases, but clinically overt pulmonary fibrosis develops in less than 10%. It is inappropriate to base treatment decisions on high-resolution CT findings in isolation, but the interpretation of lung function tests is often complicated by the coexistence of interstitial lung disease and other processes, especially pulmonary vascular disease and pleural disease.

High-resolution CT findings and lung function tests must be reconciled, with a clear definition of all complications and deconstruction of the functional defect. In this way, the degree of functional impairment ascribable to parenchymal lung disease can usually be approximately apportioned. Except in patients with a severe restrictive ventilatory defect, D_LCO levels provide the best overall guide to disease severity. Although there is no exact consensus, most clinicians regard D_LCO levels below 65% of predicted normal as indicative of clinically significant disease. In marginal cases, maximal exercise testing is often useful, as respiratory symptoms may be shown to result from musculoskeletal limitation (i.e. there is no desaturation or widening of the alveolar–arterial oxygen gradient at the limits of exercise). However, there is lingering doubt as to whether abnormalities are clinically significant in many cases and in this situation, there is no substitute for careful monitoring, with regular repetition of pulmonary function tests if treatment is not instituted immediately.

Prognostic evaluation and when to treat

The decision as to whether to start treatment is often a very close call. Many patients have intrinsically stable disease and hence the introduction of immunosuppressive therapy in attempt to prevent disease progression is often unnecessary and may result in avoidable drug toxicity.

Accurate prognostic evaluation is essential, with treatment ideally reserved for patients at higher risk of progression, but this goal is not straightforward. It is important that the few patients with predominantly inflammatory disease be identified, with a view to therapy aimed at reversing disease and restoring lung function. High-resolution CT plays a significant role in this regard: patients with organizing pneumonia and other forms of inflammatory cell infiltration are readily identifiable from characteristic high-resolution CT patterns. However, most patients have underlying irreversible interstitial fibrosis, most commonly taking the form of fibrotic NSIP. The pattern of disease at surgical biopsy can be an invaluable aide to management in the idiopathic interstitial pneumonias, but has little to offer in this respect in the rheumatological disorders, in which the distinction between NSIP and UIP seems to be less important (except, possibly, in rheumatoid arthritis). The morphological definition of interstitial fibrosis using high-resolution CT has yet to lead to reliable therapeutic recommendations.

The presence of a bronchoalveolar lavage neutrophilia in systemic sclerosis was viewed as prognostically important in patients with SSc-ILD. However, data from two large patient cohorts failed to confirm links between disease progression and neutrophilia of the bronchoalveolar lavage (BAL) fluid. Similarly, despite the fact that the prevalence of SSc-ILD is much higher in SSc subgroups positive for anti-topoisomerase antibody and anti-RNA polymerase III antibody, there is no evidence that progression of ILD differs materially according to autoantibody status.

Biomarkers can be promising prognostic tools, but for the moment no biomarker has been shown to reliably identify an increased risk of progression in CTD-ILD in a prospective study. Serum levels of KL-6 (a glycoprotein marker of lung epithelial cell turnover) correlate with the extent of systemic sclerosis-ILD and are higher in patients with active lung disease than in the remaining patients, but the prognostic value of KL-6 levels has yet to be quantified.

A staging system based on assessment of disease severity has been proposed for the identification of systemic sclerosis-ILD associated with a poorer outcome. Patients with significantly worse survival can be identified by the rapid semi-quantitative assessment of extent of disease on CT, integrated with forced vital capacity (FVC) levels.

Given the aforementioned, treatment must be based on general principles. The threshold for introducing therapy is reduced by the following three considerations:

- The risk of progression of lung disease appears to be greatest early in the course of systemic disease. In systemic sclerosis this has long been recognized, with the risk of deterioration being highest in the first 4 years. In polymyositis/dermatomyositis acute life-threatening progression of disease is much more prevalent in the first year, especially when lung disease precedes systemic disease. The same principle applies to other rheumatological disorders, although there is a paucity of data.
- Severe functional impairment has consistently been associated with a higher mortality in clinical series of rheumatological

disorders. This is best documented in systemic sclerosis, with severe reduction in D_LCO and severe lung restriction both being malignant prognostic determinants. The severity of disease becomes an increasingly important therapeutic consideration as D_LCO levels fall below 60% of predicted normal values. Severe disease requires treatment for two reasons. (1) it is indicative of a previously progressive course and an increased likelihood of future disease progression. (2) Loss of pulmonary reserve implies that the symptomatic consequences of a further preventable loss of lung function may be substantial.

- Observed disease progression is a major indication for treatment, even when the systemic disease is long-standing and the functional defect is mild to moderate. In systemic sclerosis, decline in gas transfer over 1 to 3 years is associated with a substantially increase in mortality, although it is sometimes necessary to confirm progression of lung disease (as opposed to worsening of pulmonary vascular disease) using serial high-resolution CT scanning. This is especially the case when the reduction in gas transfer is disproportionate.

In view of the absence of a definitive evidence base, management strategies can usefully be built around the recently proposed 'disease behaviour classification', developed initially for the management of unclassifiable disease (Table 18.11.4.3). More specifically, treatment decisions are informed by the designation of disease into one of five categories, based on severity, cause (if present), the predominance of reversible or irreversible disease (as judged by high-resolution CT or biopsy appearances), and the combination of this information with the observed disease behaviour.

Treatment

The treatment of interstitial lung disease in rheumatological disorders has until recently been largely empirical, consisting of traditional immunomodulation, with corticosteroid monotherapy often used in mild disease and combination therapy with low-dose corticosteroids and immunosuppressive agents (such as cyclophosphamide, azathioprine, methotrexate and mycophenolate mofetil) in more severe or progressive disease. When inflammatory disease predominates, as in organizing pneumonia or lymphocytic interstitial pneumonia, it is appropriate to treat for a therapeutic response with high-dose steroid therapy, or intense immunosuppressive therapy in refractory cases. Following a response it has been usual to gradually reduce treatment to establish the minimum dose required to prevent relapse, and in many patients with organizing pneumonia it is eventually possible to withdraw treatment altogether, although continuation of careful monitoring is advisable in the long term.

There is now ample evidence from several clinical series that this approach works well in most patients with polymyositis/dermatomyositis, with corticosteroid monotherapy often highly efficacious, although it should be stressed that high-dose corticosteroid therapy is associated with a greatly increased risk of renal crisis in systemic sclerosis and is strongly contraindicated in that disease.

Treatment decisions are less straightforward in predominantly fibrotic disease. There is lack of controlled data on treatment of these disorders, with the only current placebo-controlled trials conducted in lung disease associated with systemic sclerosis. A placebo-controlled trial of oral cyclophosphamide therapy has shown a definite treatment effect, although the inclusion of many patients with mild disease makes it difficult to draw conclusions on its clinical significance. Intravenous cyclophosphamide, given at monthly intervals, is less toxic and may be equally efficacious, based on the amplitude of the treatment effect in a placebo-controlled evaluation (although the study was underpowered). In both studies the greater part of the effect was prevention of disease progression, with regression of disease relatively infrequent. A Cochrane systematic review published in 2018 concluded that 'small benefit may be derived from the use of cyclophosphamide'.

The same broad principles are applicable in rheumatological disorders other than polymyositis/dermatomyositis and systemic sclerosis, but data remain sparse. The exception is rheumatoid arthritis-associated ILD, which is less responsive to immunosuppression. The prominent UIP pattern in this entity raises the possibility of the use of antifibrotic drugs (pirfenidone, nintedanib), as is the case in idiopathic pulmonary fibrosis, but this potential needs to be tested in clinical trials.

In a large recent retrospective series of patients with CTD-ILD, mycophenolate mofetil therapy was associated with stabilization of disease for at least 2 years in most cases. More recently a randomized control trial of cyclophosphamide versus mycophenolate mofetil in systemic sclerosis associated ILD, showed similar efficacy of the two drugs on FVC, but a greater treatment effect on gas transfer levels with mycophenolate.

Table 18.11.4.3 Disease behaviour classification

Clinical behaviour	Monitoring strategy	Treatment goal
Reversible and self-limited	To remove possible triggers	Short-term (3–6 months) observation to confirm disease regression
Reversible with risk of progression	To achieve complete or partial regression of disease and then to rationalize longer-term therapy	Short-term observation to confirm treatment response; long-term observation to ensure that gains are preserved
Stable with residual disease	To maintain status, with or without therapy	Long-term observation to assess disease course
Progressive, irreversible with potential for stabilization	To stabilize disease	Long-term observation to assess disease course
Progressive, irreversible despite treatment (i.e. a pattern of progression mimicking that of IPF)	To slow progression	Long-term observation to assess disease course and need for transplantation or effective palliation

IPF, idiopathic pulmonary fibrosis.

Some patients with interstitial lung disease associated with connective tissue disorders are refractory to conventional immunosuppression. Rituximab, a chimeric anti-CD20 monoclonal antibody, results in rapid depletion of B lymphocytes from the peripheral circulation and has shown significant clinical and functional benefit in severe, progressive CTD-ILD. Its efficacy is most impressive in patients with polymyositis/dermatomyositis, but it probably has no significant effect on progression of lung fibrosis in systemic sclerosis, and its effect in rheumatoid arthritis-associated interstitial lung disease is uncertain.

FURTHER READING

Alunno A, *et al.* (2017). Clinical, Epidemiological, and Histopathological Features of Respiratory Involvement in Rheumatoid Arthritis. *Biomed Res Int*, **2017**, 7915340. doi: 10.1155/2017/7915340.

Barnes H, *et al.* (2018). Cyclophosphamide for connective tissue disease-associated interstitial lung disease. *Cochrane Database Syst Rev*, **1**:CD010908. doi: 10.1002/14651858.CD010908.pub2.

Bouros D, *et al.* (2002). Histopathological subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. *Am J Respir Crit Care Med*, **165**, 1581–6.

Corte TJ, Du Bois RM, Wells AU. (2015). Infiltrative and interstitial lung diseases: connective tissue diseases. In: Broaddus VC, *et al.* (eds). *Murray and Nadel's Textbook of Respiratory Medicine*, 6th edn, pp. 1165–87. Elsevier Saunders, Philadelphia.

DeMarco PJ, *et al.* (2002). Predictors and outcomes of scleroderma renal crisis: the high-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis trial. *Arthritis Rheum*, **46**, 2983–9.

El Hadidi KT, *et al.* (2018). Characteristics of systemic lupus erythematosus in a sample of the Egyptian population: a retrospective cohort of 1109 patients from a single center. *Lupus*, **27**, 1030–8.

Elhai M, *et al.* (2019). Outcomes of patients with systemic sclerosis treated with rituximab in contemporary practice: a prospective cohort study. *Ann Rheum Dis*, **78**, 979–87.

Friedman AW, Targoff IN, Arnett FC (1996). Interstitial lung disease with autoantibodies against aminoacyl-tRNA synthetases in the absence of clinically apparent myositis. *Semin Arthritis Rheum*, **26**, 459–67.

Haupt HM, Moore GW, Hutchins G (1981). The lung in systemic lupus erythematosus. Analysis of the pathologic changes in 120 patients. *Am J Med*, **71**, 791–8.

Hoyles RK, Wells AU (2007). Pulmonary fibrosis in collagen vascular diseases. In: Costabel U, du Bois RM, Egan JJ (eds). *Diffuse parenchymal lung disease*. Basel, Karger, pp. 185–96.

Hoyles RK, *et al.* (2006). A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum*, **54**, 3962–70.

Hyland RH, *et al.* (1983). A systematic controlled study of pulmonary abnormalities in rheumatoid arthritis. *J Rheumatol*, **10**, 395–405.

King TE, Kim EJ, Kinder BW (2011). Connective tissue disease. In: Schwarz MI, King TE (eds) *Interstitial lung disease*, 5th edn, pp. 689–764. People's Medical Publishing House, USA.

Marie I, *et al.* (1998). Pulmonary involvement in polymyositis and dermatomyositis. *J Rheumatol*, **25**, 1336–43.

Papiris SA, *et al.* (1999). Lung involvement in primary Sjögren's syndrome is mainly related to the small airways disease. *Ann Rheum Dis*, **58**, 61–4.

Roofeh D, *et al.* (2019). Management of systemic sclerosis-associated interstitial lung disease. *Curr Opin Rheumatol*, **31**, 241–9.

Tashkin DP, *et al.* (2006). Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med*, **354**, 2655–66.

18.11.5 The lung in vasculitis

G.A. Margaritopoulos and A.U. Wells

ESSENTIALS

Lung involvement in vasculitic disease can manifest as diffuse alveolar haemorrhage or as other pulmonary vasculopathy. Presenting features of diffuse alveolar haemorrhage include fever, weight loss, and other systemic symptoms in association with cough, breathlessness, and clinical signs suggestive of pneumonia. Haemoptysis may be present but is not invariable. A fall in haemoglobin over a day or longer suggests the diagnosis, and bronchoalveolar lavage is usually diagnostic. Other pulmonary vasculopathies present with breathlessness on exertion. Investigation reveals isolated reduction in gas transfer (carbon monoxide diffusing capacity), with or without pulmonary hypertension.

Many vasculitic disorders can affect the lung, most notably including (1) eosinophilic granulomatosis with polyangiitis (previously known as Churg–Strauss syndrome)— typified by rhinitis with nasal polyps and treatment-resistant late-onset asthma followed, with chest radiography shows patchy lung infiltration in up to 80% of patients. (2) Granulomatosis with polyangiitis (previously known as Wegener's granulomatosis)—chronic rhinitis, sinusitis, or mastoiditis is typically followed by progression to generalized disease over months to years. The main lung manifestations are with pulmonary nodules (which can cavitate), localized or diffuse infiltrates, alveolar haemorrhage that may be part of a pulmonary–renal syndrome, and large and small airway disease.

Management—limited disease is generally treated with oral corticosteroid, given as monotherapy or in combination with a second-line immunosuppressive agent. Oral corticosteroid with either cyclophosphamide or rituximab are typically used to induce remission of generalized disease. Azathioprine or methotrexate with low dose oral prednisolone are used to maintain remission.

Introduction

It is useful to subdivide pulmonary vasculitides into primary systemic or secondary, and to differentiate them from nonvasculitic disorders that can affect the pulmonary circulation, listed in Table 18.11.5.1. The secondary and nonvasculitic diseases are discussed in other chapters: Table 18.11.5.2 summarizes the primary

Table 18.11.5.1 Pulmonary vascular disease

Vasculitic	Nonvasculitic
Primary systemic	Thromboembolic
Secondary	Primary pulmonary hypertension
• Rheumatological	Secondary pulmonary hypertension
• Pulmonary–renal	Systemic sclerosis
• Behçet's syndrome	Idiopathic pulmonary haemosiderosis
• Chronic infection	Arteriovenous malformations
• Lymphoma	
• Drugs	
Penicillamine	
Hydralazine	
Propylthiouracil	
Nitrofurantoin	

vasculitides, indicating those in which the lung is involved. According to Chapel Hill International's nomenclature (2012 revision), Churg–Strauss syndrome and Wegener's granulomatosis have been renamed as eosinophilic granulomatosis with polyangiitis (EGPA) and granulomatosis with polyangiitis (GPA), respectively.

Clinical manifestations of pulmonary vasculitis

Lung involvement in vasculitic disease can manifest as:

- diffuse alveolar haemorrhage;
- an isolated reduction in gas transfer (carbon monoxide diffusing capacity, $D_L$co), with or without pulmonary hypertension.

Investigations listed in Box 18.11.5.1 should be performed if pulmonary vasculitis is suspected.

Table 18.11.5.2 2012 revised International Chapel Hill consensus nomenclature of systemic vasculitis

Systemic vasculitis	Lung disease
• Large vessel	
Giant cell arteritis	Rare
Takayasu's arteritis	Frequent
• Medium-size vessel	
Polyarteritis nodosa	Rare
Kawasaki disease	No
• Small vessel (medium-size vessel involvement may be present)	
Granulomatosis with polyangiitis	Frequent
Eosinophilic granulomatosis with polyangiitis	Frequent
Microscopic polyangiitis	Frequent
Henoch–Schönlein purpura	No
Essential cryoglobulinaemia	No

Box 18.11.5.1 Investigations to be considered if lung vasculitis is suspected

Imaging
- Chest radiography and high-resolution CT

Lung function tests
- $D_L$co/Kco

Blood gases

Renal function
- Urine dipstick testing and microscopy for proteinuria, haematuria, and cellular casts; measurement of serum creatinine; consider renal biopsy (if evidence of nephritis)

Immunology
- Antineutrophil cytoplasmic antibodies (ANCA), antiglomerular basement membrane (anti-GBM) antibodies, immune complexes, rheumatoid factor, antinuclear antibodies, antiphospholipid antibodies

Bronchoscopy/Bronchoalveolar lavage
- Iron-laden macrophages
- Exclusion of low tract respiratory infections
- Assessment of the large airways (stenosis-endobronchial lesion)

Biopsy
- Renal
- Skin
- Lung (surgical)

Diffuse alveolar haemorrhage

The presenting features of diffuse alveolar haemorrhage include fever, weight loss, and other systemic symptoms in association with cough, breathlessness, and clinical signs suggestive of pneumonia. A history of previous haemoptysis is sometimes helpful, but in other cases diffuse alveolar haemorrhage presents acutely. Chest radiography shows consolidation, typically resolving within a matter of days, unlike the usual time-course in infective pneumonia. High-resolution CT may reveal an extensive ground-glass appearance, denoting partial alveolar filling. A fall in haemoglobin over a day or longer is diagnostically useful, and chronic iron-deficiency anaemia can arise from low-grade haemorrhage over a lengthy period.

Bronchoalveolar lavage is usually diagnostic in the absence of haemoptysis, revealing overt blood staining in sequential lavage in the acute presentation, or the presence of numerous macrophages containing iron, identified by Perl's stain, in chronic disease. The gas transfer corrected for alveolar volume (Kco) is elevated in acute haemorrhage, but only if measured within 36 h, seriously limiting the diagnostic yield. Diffuse pulmonary haemorrhage occurring without identifiable cause or association is known as idiopathic pulmonary haemosiderosis (see Chapter 18.14.1).

Isolated gas transfer deficit, with or without pulmonary hypertension

Pulmonary vasculopathies other than alveolar haemorrhage present with breathlessness on exertion. Clinical examination of the respiratory system and routine lung imaging are normal. Lung function tests show preservation of lung volumes with an isolated reduction of $D_L$co. In severe pulmonary vascular disease pulmonary hypertension may be clinically overt, and in other cases it is detected by echocardiography, especially if tricuspid regurgitation allows Doppler

estimation of pulmonary artery pressures. Vasculopathies other than vasculitis should be considered in this clinical context, including ablative vasculopathies (as in systemic sclerosis and primary pulmonary hypertension) and coagulopathies leading to thromboembolism or intrapulmonary microvascular thrombosis (see Chapter 16.15.2).

The following sections discuss lung involvement in specific vasculitic disorders, followed by discussion of key clinical problems, prognosis, and treatment.

Eosinophilic granulomatosis with polyangiitis

First described by Churg and Strauss in 1951, this rare condition has an estimated annual incidence of approximately 3 per million and mostly affects adults aged 30 to 50 (although the reported age range is 7–74 years). There is no strong gender predilection. Typically, asthma and eosinophilia are associated with the characteristic histological findings (Fig. 18.11.5.1), consisting of profuse eosinophilic infiltration, extravascular granulomatous inflammation, and necrotizing arteritis affecting small to medium-sized vessels. There is little information about geographical variation.

Aetiology and pathogenesis

The underlying pathogenetic mechanism is generally considered to be an eosinophilic granulomatous response to a foreign antigen, akin to the eosinophilic granulomatosis seen in schistosomiasis. In support of this hypothesis, immunological stimuli (vaccination or immunotherapy) have been reported to trigger the disease, although the pauci-immune nature of the histopathology has yet to be explained. The introduction of antileukotriene therapy for asthma has been associated with an increased incidence of EGPA, but it remains unclear whether the drug triggers the onset of disease. It is also possible that reduction or withdrawal of corticosteroids with better control of asthma unmasks the condition in some cases, although some individuals who have never received corticosteroids have developed the syndrome with the introduction of an antileukotriene agent.

The HLA-DRB1*04 and *05 alleles and the related HLADRB4 gene are associated with increased risk of developing EGPA. There is evidence suggesting that the disease is mediated by a Th-2 response through the release of cytokines such as IL-4,-13,-5. Th1 and Th17 cells are involved in advanced stages, whereas T regulatory cells are reduced in active disease. It has recently been proposed that B-cells can contribute to the development of the disease.

Antineutrophil cytoplasmic antibodies (ANCA), first described in 1982, are frequently present in systemic vasculitides involving small and medium-sized vessels, including EGPA, GPA, and microscopic polyangiitis. ANCA are directed against cytoplasmic antigens in polymorphonuclear leucocytes and monocytes and are subcategorized according to their immunofluorescent staining pattern as C (cytoplasmic), P (perinuclear), or A (atypical). The pathogenetic significance of ANCA is unclear, but ANCA receptors on the surface of neutrophils are upregulated at disease sites, and ANCA can also interact with endothelial cells to cause injury and coagulation. All ANCA patterns have been reported in EGPA, but P-ANCA occur most frequently, usually directed against myeloperoxidase (MPO) and only very infrequently against proteinase 3 (PR3).

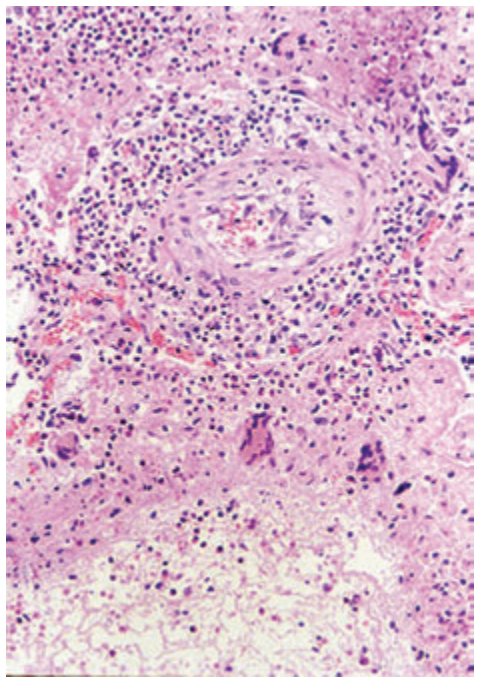

Fig. 18.11.5.1 A case of eosinophilic granulomatosis with polyangiitis showing a pulmonary artery surrounded by granulomatous inflammation and a florid mixed inflammatory cell infiltrate that includes abundant eosinophils.

Pulmonary presentation and diagnostic criteria

Two sets of diagnostic criteria have been used: Lanham's criteria and the criteria of the American College of Rheumatology.

In addition to systemic features such as fever and weight loss, Lanham defined the disease as requiring:

- asthma
- eosinophilia greater than 1.5×10^9/litre in the peripheral blood
- evidence of systemic vasculitis in two or more organs other than the lung

The American College of Rheumatology definition requires the satisfaction of at least four of the following six criteria:

- the presence of asthma
- eosinophilia greater than 10% in the peripheral blood
- evidence of a neuropathy in a vasculitic pattern (e.g. mononeuritis multiplex)
- transient pulmonary infiltrates
- a history of sinus disease
- evidence of extravascular eosinophilia on biopsy

In most patients asthma precedes vasculitic manifestations, often by years, although these features develop simultaneously in up to 20% of cases. Typically the prodromal phase consists of rhinitis with nasal polyps, which often lasts for years before the eventual development of late-onset asthma that is generally resistant to treatment. The second phase is characterized by eosinophilia in the peripheral blood and tissues and often follows a relapsing and remitting course. The final phase, systemic vasculitis, often follows the onset of the

second phase by several years and is immediately preceded by improvement in asthma. This pattern of evolution of disease is more than 95% specific and sensitive for EGPA. Respiratory failure and status asthmaticus account for 10% of deaths.

Other organ involvement

Skin lesions

These are seen in about 60% of patients, generally manifesting as palpable purpura or subcutaneous nodules. Skin infarcts also occur.

Cardiac involvement

The heart may be involved diffusely, producing congestive cardiac failure or restrictive cardiomyopathy. Eosinophilic myocarditis is present in up to 50% of cases, with coronary artery vasculitis and pericardial effusions much less frequent. Cardiac disease is the most common cause of death.

Renal disease

This is much less common than in GPA or microscopic polyangiitis, but the histopathology is very similar, consisting of a focal segmental necrotizing glomerulonephritis. Renal disease is generally mild, but end stage renal failure is reported. See Chapter 21.10.2 for further discussion.

Nervous system involvement

Mononeuritis multiplex such as drop wrist or drop foot, confirmed by nerve conduction studies or sural nerve biopsy, is the most common manifestation, occurring in up to 75% of patients. Cranial nerve involvement is less common, but cerebrovascular disease may occur.

Gastrointestinal involvement

Vasculitis of the mesenteric vessels may produce bowel abnormalities, including perforation, and less commonly eosinophilic infiltration may cause obstruction.

Musculoskeletal system

Arthritis is relatively common, as are myalgias.

Investigation

Chest radiography shows patchy lung infiltration in up to 80% of patients and pleural disease is present in up to 50%. High-resolution CT is much more sensitive than chest radiography, although the full spectrum of abnormalities has yet to be defined. The most frequent findings are patchy ground-glass infiltration and patchy consolidation. An extensive ground-glass appearance is usual in patients in whom alveolar haemorrhage is due to capillaritis, whereas consolidation is more suggestive of granuloma formation in association with involvement of medium-sized vessels. Pulmonary infiltrates are much more common than pulmonary nodules and, in contrast to GPA, cavitation of nodules is extremely rare. Bronchial wall thickening and bronchiectasis have also been described. Table 18.11.5.3 lists the major pulmonary manifestations.

There is a peripheral blood eosinophilia, matched by a marked eosinophilia on bronchoalveolar lavage. The diagnostic role of ANCA continues to be debated. ANCA, usually P-ANCA-MPO, are present in up to two-thirds of patients, but in some series their prevalence is much lower and P-ANCA also occur in many other nonvasculitic autoimmune and infectious conditions. Thus, the presence of P-ANCA is no more than a useful ancillary finding, increasing the diagnostic likelihood, and the absence of P-ANCA should not materially influence the diagnostic algorithm. ANCA-positive patients more frequently have peripheral neuropathy, glomerulonephritis, and purpura compared to ANCA negative patients, who have more frequent lung, myocardial, and gastrointestinal symptoms.

Table 18.11.5.3 Distinguishing thoracic features in primary vasculitis

Thoracic features	Eosinophilic granulomatosis with polyangiitis	Granulomatosis with polyangiitis	Microscopic polyangiitis
Subglottic stenosis		+	+
Multiple nodules	+	+	
Solitary nodules		+	
Cavities		+	
Localized infiltrates		+	+
Transient infiltrates	+		+
Pleural involvement	+	+	
Cardiac involvement	+		

Eotaxin-3, an eosinophil attracting chemokine, could be an attractive biomarker for the future, as at a cut-off level of 80 pg/ml it has a sensitivity and specificity of 87.5% and 98.6%, respectively, to diagnose active EGPA.

The classical triad at lung biopsy consists of necrotizing angiitis, granulomas, and tissue eosinophilia (Fig. 18.11.5.1). Giant cells and fibrinoid necrosis are present. However, it is not uncommon for histological appearances to be indeterminate, with the presence of some but not all of the characteristic features, and in some cases there is overlap with the histopathological appearances of GPA or microscopic polyangiitis. Surgical biopsies have a much higher diagnostic yield than transbronchial biopsies, which seldom disclose vasculitis.

Granulomatosis with polyangiitis

The systemic features of GPA are described in Chapter 19.11.7. It is the third most prevalent systemic vasculitis (after giant cell arteritis and vasculitis in rheumatoid arthritis), and occurs throughout the world with an annual incidence of 3–11 per million, depending upon the geographic region. It mainly affects adults aged 30–50 (although it may occur in any age group), and there is no gender predilection. The histological abnormalities consist of granulomatous inflammation associated with necrotizing vasculitis, affecting small to medium-sized vessels (Fig. 18.11.5.2). Lung involvement occurs at some stage of disease in up to 85% of cases; upper respiratory tract and renal involvement (due to necrotizing glomerulonephritis) are frequent.

Aetiology and pathogenesis

Studies of possible genetic associations have yielded conflicting results, with linkage to HLA DR1 or HLA DR2 in some but not all

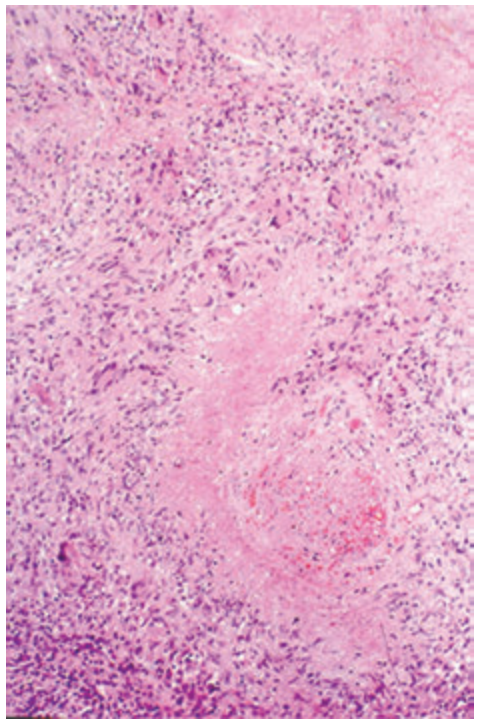

Fig. 18.11.5.2 A case of granulomatosis with polyangiitis (GPA) showing an area of geographic necrosis around a partly destroyed pulmonary vessel. This focus is surrounded by chronic inflammation and fibrosis, within which there is granulomatous inflammation with the giant cells showing a somewhat pyramidal morphology.

populations. The importance of environmental factors is equally uncertain. Case–control studies have suggested that exposure to silica or silicone might be pathogenetic in some cases. ANCA-positive vasculitis mimicking GPA has been induced by propylthiouracil, hydralazine, and penicillamine, possibly by modifying MPO and thereby creating an antigenic stimulus. However, the most suggestive data relate to infection, especially with *Staphylococcus aureus*. Chronic nasal carriage of *S. aureus* is substantially more prevalent in GPA than in control populations, and it has been suggested that staphylococcal acid phosphatase might be antigenic in susceptible individuals. An immunostimulatory role for *S. aureus* B-cell superantigens has also been proposed. The partial efficacy of prophylactic trimethoprim–sulfamethoxazole in reducing both infection and the likelihood of relapse of GPA provides further indirect support for an infectious pathogenesis.

Pathogenetic concepts are complicated by the histological spectrum of disease, ranging from prominent granulomatous lesions, associated with a lymphocytosis on bronchoalveolar lavage, to fulminant necrotizing vasculitis, in which a bronchoalveolar lavage neutrophilia is the rule. The genesis of granulomata is not well understood, but there is strong indirect evidence that neutrophils play a key role in initiating vasculitis. PR3 is the main target antigen for C-ANCA, which is found in about 90% of patients with generalized GPA (as compared to 50% of patients with localized disease). As in other ANCA-positive vasculitides, there is *in vitro* and animal model evidence to suggest that PR3-ANCA might interact with primed neutrophils, leading to neutrophil degranulation and thus to endothelial damage and further neutrophil recruitment.

Pulmonary presentation

Involvement of the upper and/or lower respiratory tract is the presenting feature in 90% of cases. Disease usually evolves in two phases. Initially there is chronic rhinitis, sinusitis, or mastoiditis, after which most patients progress to generalized disease over months to years, with lower respiratory tract involvement in 65 to 85% often manifesting with cough, which may be purulent, and less frequently with haemoptysis due to diffuse alveolar haemorrhage. Systemic symptoms, including fever and weight loss, are frequent in generalized disease, along with variable involvement of other organs as described in Chapter 19.11.7. Lung involvement is asymptomatic in about one-third of cases, with the main lung manifestations being (see **Table 18.11.5.3**):

- one or more nodules, which can cavitate (**Fig. 18.11.5.3a**)
- localized or diffuse infiltrates (**Fig. 18.11.5.3b**)
- alveolar haemorrhage that may be part of a pulmonary–renal syndrome
- large and small airway disease

Investigations

As in other vasculitides, classical features are not always present at biopsy, with many patients having only one or two of the three cardinal histological features (granuloma, necrosis, vasculitis). If a lung

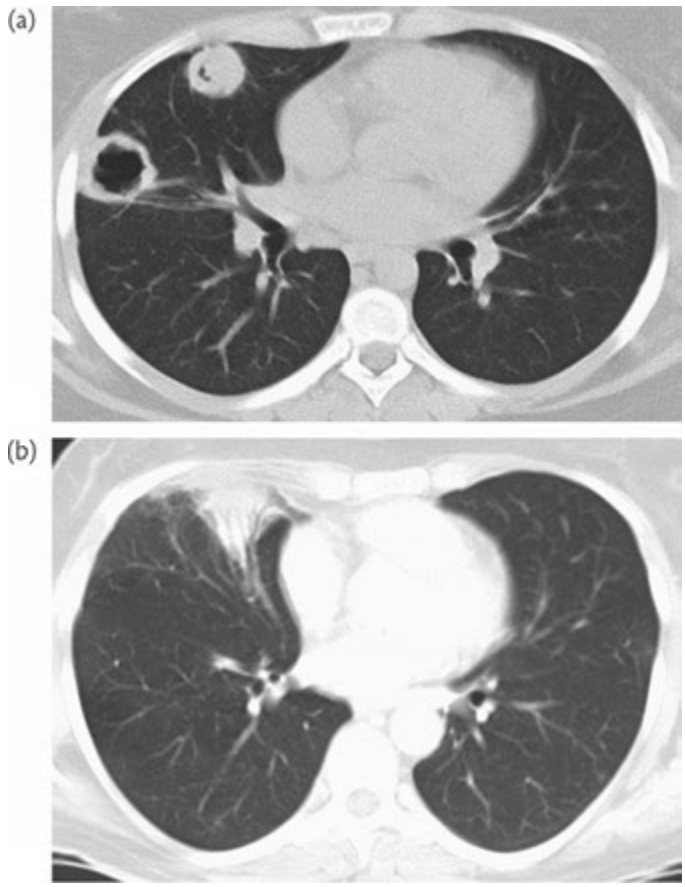

Fig. 18.11.5.3 GPA most often presents radiologically. CT scans may reveal one or more nodules, which can cavitate (a), or localized (b) or diffuse infiltrates.

biopsy is required, surgical biopsy is preferred, transbronchial biopsies having a much lower diagnostic yield, especially when not targeted to areas with overt abnormalities on chest radiography or high-resolution CT. In advanced pulmonary disease the hazards of biopsy should prompt a search for an alternative biopsy site, including the kidney, skin, and skeletal muscles. Endoscopic nasal biopsy appearances are most often nonspecific, although positive features in a few cases provide a definitive diagnosis. Irrespective of the biopsy site, suggestive appearances may be diagnostic when combined with clinical and serological information even when diagnostic histological features are absent.

The two main patterns on chest radiography and high-resolution CT are nodules and consolidation, with pleural effusions an occasional finding. High-resolution CT offers the important advantage of better definition of nodule cavitation, a key diagnostic feature, and may also disclose abnormalities of the large intrathoracic and extrathoracic airways, including subglottic stenosis, stenosis of large airways, and bronchiectasis. Subglottic stenosis is present in up to 25% of cases and can develop without concomitant systemic disease activity.

Fibre-optic bronchoscopy may show tracheobronchitis, including ulceration and 'cobblestoning' of the mucosa, or airway stenosis. Bronchoalveolar lavage fluid contains an excess of neutrophils and usually of eosinophils (with diffuse infiltrates) or lymphocytes (more interstitial disease), but is most useful in excluding alveolar haemorrhage or infection, including opportunistic infection in treated patients.

Haematological and biochemical investigations reflect the inflammatory process. The diagnosis should never be based upon C-ANCA positivity in isolation because these are also found in other contexts, including other vasculitides, chronic bacterial infections, and cryoglobulinaemia.

Microscopic polyangiitis

The main description of microscopic polyangiitis occurs elsewhere (Chapter 19.11.7), but this necrotizing vasculitis affects small to medium-sized vessels, with few or no immune complex deposits, and lung disease occurs in 35–55% of cases.

Pulmonary presentation

Lung involvement is less frequent than in GPA. The major presentation (Table 18.11.5.3) is diffuse alveolar haemorrhage, which can have a poor prognosis. Pulmonary capillaritis may be associated with evidence of disease outside the lung, particularly necrotizing glomerulonephritis, mononeuritis multiplex, and skin lesions.

It is often difficult to distinguish microscopic polyangiitis from GPA clinically. The key histological distinction is the absence of granulomas, which are characteristically present in GPA. Renal biopsies can be identical in the two conditions. Microscopic polyangiitis also needs to be distinguished from polyarteritis nodosa that, by definition, only affects arteries, rarely arterioles, and never small vessels. Renal vasculitis with microaneurysm formation occurs in polyarteritis nodosa but not microscopic polyangiitis, and diffuse alveolar haemorrhage does not occur in polyarteritis nodosa.

Other diseases

Other primary systemic vasculitides occasionally present with respiratory features.

Takayasu's arteritis

This arteritis affects predominantly the aorta and its main branches but involves the pulmonary arteries in up to 50% of patients, presenting with pulmonary vascular occlusion.

Giant cell arteritis

There is rarely objective evidence of lung involvement, but 25% of patients with giant cell arteritis have cough, hoarseness, and sore throat at presentation.

The other systemic vasculitides that feature in the Chapel Hill International consensus nomenclature, but which rarely, if ever, present with lung disease, are Henoch–Schönlein purpura and essential cryoglobulinaemia.

Behçet's disease

This occurs predominantly in Mediterranean countries and can produce pulmonary vascular inflammation affecting all sizes of vessels and resulting in pulmonary arterial aneurysms, arterial and venous thrombosis, pulmonary infarcts, and pulmonary haemorrhage. It is crucial to differentiate haemorrhage from thrombosis because of the treatment implications.

Pulmonary veno-occlusive disease

This is a disorder of unknown cause that manifests with progressive occlusion of the postcapillary venules, resulting in features similar to those of pulmonary oedema. There is no known effective treatment. Differentiation from cardiogenic causes of raised pulmonary venous pressure must be made.

Key clinical problems in vasculitis

Diagnosis

Ideally, typical histological appearances should be present, and when they are not present the requisite number of clinical criteria should be met. However, formal diagnostic criteria are merely a basis for diagnostic negotiation in many cases. Classification systems fail to capture the entire spectrum of vasculitic disease, with many patients having features overlapping between diagnostic entities. With the advent of ANCA antibodies, *formes frustes* of full blown vasculitic syndromes are increasingly diagnosed, with transient or no fulfilment of full diagnostic criteria in many instances. Even in cases satisfying diagnostic criteria, the clinical heterogeneity of the vasculitic syndromes is notorious, it often being stated that no two patients are alike.

An appreciation of these difficulties informs the clinician of the need for a versatile diagnostic approach. When vasculitis is suspected but full clinical criteria are not satisfied, a histological diagnosis should generally be sought, targeted to involved organs. Failure to capture typical appearances at biopsy does not necessarily exclude a diagnosis of vasculitis as vasculitic processes may be patchy and nonspecific inflammatory change may be evident: this

applies especially to upper airway biopsies in patients with GPA. An empirical diagnosis of a vasculitic syndrome must sometimes be made, and in these cases—which tend to foment a great deal of insecurity in patients and clinicians alike—it is essential to do everything possible to exclude the most frequent differential diagnoses, namely infection and malignancy.

When formal diagnostic criteria for a vasculitic syndrome are not fulfilled and empirical treatment is required, the general approach—including initial treatment and monitoring—should be as for the vasculitic syndrome most closely resembling the particular clinical presentation of the patient. When the diagnosis is uncertain the initial treatment should be definitive because a satisfactory response provides useful ancillary diagnostic support ('diagnosis by therapeutic challenge'): a tentative initial therapeutic approach often merely serves to prolong diagnostic uncertainty.

Prognosis

The outcome of the more frequent vasculitic syndromes was poor when they were first described, but has improved strikingly, as best illustrated by the mortality of GPA: the mean survival of 5 months in early reports has now been transformed, with complete initial remission in 75% of cases, increasing further with the recent use of rituximab. However, despite these improvements, long-term follow-up continues to be needed in GPA (relapse occurs in 50–70% of cases) and other vasculitides.

The improvement in prognosis in GPA, also seen in EGPA, in part reflects the increasing use of immunosuppressive agents in combination with corticosteroid therapy. However, the increasing detection of milder disease, including patients with limited involvement, has also undoubtedly improved average outcome. Localized GPA has a better outcome than disease with multiorgan involvement. The prognosis of EGPA is generally good for those with isolated intrathoracic disease (5-year survival 88%), but worsens with two or more extrapulmonary complications (5-year survival 54%), particularly with proteinuria more than 1 g/day, renal insufficiency (creatinine >140 μmol/litre), cardiomyopathy, gastrointestinal disease, or central nervous system involvement.

The causes of death in vasculitis can be broadly subdivided into sepsis (as a complication of treatment) and disease progression. In GPA death from progressive disease is most commonly due to renal failure or lung involvement. In EGPA the main cause of death is cardiac disease, followed by renal failure, cerebrovascular involvement, and gastrointestinal disease, with lung disease accounting for 10% of deaths.

Treatment

As a general rule, treatment of vasculitis includes two phases: induction of remission with aggressive therapy against vasculitis; and maintenance of remission with the aim of establishing the minimum level of therapy required to prevent relapse. The choice of treatment is based on the activity and extent of disease (**Table 18.11.5.4**).

Limited disease

Treatment recommendations are based mainly on expert opinion, given the lack of clinical trials. Immunomodulation with oral corticosteroid, given as monotherapy or in combination with a second-line immunosuppressive agent such as methotrexate, azathioprine, or mycophenolate mofetil is the most frequent regimen used in this group of patients.

Table 18.11.5.4 EUVAS (European Vasculitis Study Group) classification

EUVAS classification	Clinical features
Limited	Isolated upper airways disease
Early generalized	End-organ involvement that lacks a clear or immediate threat to organ function
Generalized active	End-organ involvement with clinically significant impairment of organ function
Severe	Immediate threat of organ failure or death
Refractory	Disease that was failed to respond to conventional therapies
Remission (maintenance)	No evidence of ongoing vasculitic activity

Early generalized disease

The combination of corticosteroid and cyclophosphamide is most often used to induce remission. Methotrexate at a dose of 0.3/mg/kg/week has less side effects and is better tolerated than cyclophosphamide, but is associated with a higher rate of relapse.

Generalized active disease

The combination of oral corticosteroids and oral cyclophosphamide achieves remission in 55–80% of cases. The initial dose of oral steroids is 1 mg/kg/day, but in more severe cases intravenous administration at the dose of 7.5–15 mg/kg/day for 1–3 consecutive days is preferred. A major benefit of initial pulsed therapy is that lower doses of oral corticosteroids can subsequently be used in rapid responders, thus minimizing long-term steroid-related side effects such as infections, diabetes, and osteoporosis. Treatment with steroids should be carried on for at least 6–12 months after the initial presentation of the disease as earlier discontinuation is associated with an increased risk of relapse.

Cyclophosphamide can be administered orally (2 mg/kg/day) or intravenously (600 mg/m^2 at three- to four-weekly intervals), depending on disease severity. The side effects include neutropenia and infections, haemorrhagic cystitis, late bladder cancer, and infertility (with bladder side effects less prevalent with the use of intravenous regimens). Intravenous cyclophosphamide is also less toxic with regard to other side effects, but is associated with a higher rate of relapse compared to oral cyclophosphamide.

Rituximab, an anti-CD20 monoclonal antibody, was initially used to treat relapsing disease (375 mg/m^2 weekly for four weeks). More recently, it has proved to be more effective than oral cyclophosphamide for induction of remission, used in combination with steroid therapy, and equally effective in the treatment of alveolar haemorrhage. When rituximab is used to induce remission, it is often possible to avoid or minimize maintenance therapy, offering an important advantage of over cyclophosphamide-based induction regimens. Taken together, trial data and accumulated clinical experience suggest that rituximab may be superior to cyclophosphamide as induction therapy, although not always approved for use due to cost considerations. Rituximab is the agent of choice when there are contraindications to cyclophosphamide and for relapse following cyclophosphamide therapy (especially

when there is a high cumulative oral cyclophosphamide dose), and when there are concerns about infertility with the use of cyclophosphamide.

Severe disease

In severe disease with diffuse alveolar haemorrhage or renal failure, plasma exchange should be considered early, together with high doses of intravenous methyl-prednisolone and cyclophosphamide. In cases of life-threatening disease at presentation, the use of initial combination intravenous therapy with methyl-prednisolone, cyclophosphamide, and rituximab should be considered, especially if plasma exchange is not available.

Refractory disease

Intravenous immunoglobulin has been used in refractory disease, particularly in the setting of recurrent infections and in pregnant woman who cannot receive immunosuppressive agents. This treatment is less toxic than the regimens described here, but is contraindicated in patients with severe renal disease (creatinine level >300 μmol/l).

Maintenance of remission

For the maintenance of remission, azathioprine (2 mg/kg/day) has been used after 3–6 months' treatment with cyclophosphamide, reducing total exposure to cyclophosphamide without an increase in the rate of relapse. Methotrexate at a dose of 25 mg/week is as efficacious as azathioprine as maintenance therapy. Mycophenolate mofetil is associated with a higher rate of relapse than methotrexate or azathioprine and is not recommended as second-line therapy. It is usual practice to combine azathioprine or methotrexate with low dose oral prednisolone (e.g. 5–10 mg daily). In general, maintenance treatment should be continued for at least 18 months and must often be used for many years, but long-term treatment decisions can only be made on a case by case basis.

Prophylactic co-trimoxazole (trimethoprim 160 mg/ sulfamethoxazole 800 mg three times weekly) is often recommended when long-term intense immunomodulation has been instituted to prevent opportunistic infection by *Pneumocystis jirovecii*. It has been efficacious in suppressing disease activity in GPA patients with localized upper respiratory tract or minor lower respiratory tract disease, but does not have an established ancillary role in aggressive systemic disease, although usually justifiable in this context as antipneumocystis prophylaxis.

FURTHER READING

Frankel SK, *et al.* (2012). The pulmonary vasculitides. *Am J Respir Crit Care Med*, **186**, 216–24.

Greco A, *et al.* (2015). Churg–Strauss syndrome. *Autoimmun Rev*, **14**, 341–8.

Guillevin L, *et al.* (1996). Prognostic factors in polyarteritis nodosa and Churg–Strauss syndrome. A prospective study in 342 patients. *Medicine*, **75**, 17–28.

Jayne D, *et al.* (2003). A randomized trial of maintenance therapy for vasculitis associated with antineutrophil cytoplasmic autoantibodies. *New Engl J Med*, **349**, 36–44.

Jennette JC, *et al.* (2013). 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum*, **65**, 1–11.

Keogh KA, *et al.* (2006). Rituximab for refractory Wegener's granulomatosis: report of a prospective, open-label pilot trial. *Am J Respir Crit Care Med*, **173**, 180–7.

Lanham JG, *et al.* (1984). Systemic vasculitis with asthma and eosinophilia: the clinical approach to the Churg–Strauss syndrome. *Medicine (Baltimore)*, **63**, 65–81.

Lhote F, Guillevin L (1998). Polyarteritis nodosa, microscopic polyangiitis and Churg–Strauss syndrome. *Semin Respir Crit Care Med*, **19**, 27–46.

Nguyen Y, Guillevin L. (2018). Eosinophilic granulomatosis with polyangiitis (Churg-Strauss). *Semin Respir Crit Care Med*, **39**, 471–81.

Pagnoux C, Guillevin L (2015). Treatment of granulomatosis with polyangiitis (Wegener's). *Expert Rev Clin Immunol*, **11**, 339–48.

Specks U (2011). Pulmonary vasculitis. In: Schwarz MI, King TE Jr (eds). *Interstitial lung disease*, 5th edn, pp. 765–804. People's Medical Publishing House, USA.