Vasculitis and Rare Lung Diseases

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Introduction

The European Respiratory Society's White Book defines a rare disease as a disorder affecting less than 1 in 2000 of the population [1]. The terms "rare lung disease" and "orphan lung disease" are frequently used interchangeably, but they are not identical. Orphan lung diseases are those that tend not to receive attention in the research community and for which there may be no specific treatment. Patients may experience delay in diagnosis or in accessing expertise in managing their condition, and may feel abandoned in the world of healthcare. Not all rare lung diseases will be orphan lung diseases and not all orphan lung diseases with be rare lung diseases (e.g. parasitic infections). This chapter will concentrate on the rare lung diseases listed in Table 17.1.

Table 17.1 The principal rare lung diseases

Pulmonary vasculitis
Granulomatosis with polyangiitis (Wegener's)
Microscopic polyangiitis
Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)
Behçet's disease
Takayasu's arteritis
Autoimmune diseases
Anti-basement membrane syndrome
Pulmonary alveolar proteinosis
IgG4 related lung disease
Disorders of genetic origin
Lymphangioleiomyomatosis associated with tuberous sclerosis
Multiple cystic lung disease in Birt–Hogg–Dubé syndrome
Other rare diseases
Thoracic endometriosis
Langerhans cell histiocytosis
Idiopathic pulmonary haemosiderosis

Adapted from Gibson GJ, Loddenkemper R, Lundbäck B, Sibille Y, editors. Rare and orphan lung disease. In: European Lung White Book. Sheffield, UK: European Respiratory Society; 2013

Pulmonary Vasculitis

The vasculitides are a heterogeneous group of multisystem diseases that are characterised by a triad of inflammation, damage to the vessel wall, and impaired blood flow with ensuing local tissue injury. The clinical presentation of these vasculitides is defined by the site, type, and size of the vessel and pathological pattern of vessel injury, as shown in Table 17.2.

In light of recent advances in the understanding of the aetiology and pathogenesis of these disorders, their nomenclature was modified at the International Chapel Hill Consensus Conference

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Table 17.2 The features of the main pulmonary vasculitides

Vessel size	International Chapel Hill consensus conference definitions 2012
Small vessel	
Granulomatosis with polyangiitis (Wegener's) (GPA)	*Necrotizing granulomatous inflammation* usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)	*Eosinophil-rich and necrotizing granulomatous* inflammation often involving the respiratory tract, associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present
Microscopic polyangiitis (MPA)	*Necrotizing vasculitis*, with few or no immune deposits, predominantly affecting small vessels. Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. *Granulomatous inflammation is absent*
Anti–glomerular basement membrane (anti-GBM) disease	*Vasculitis affecting glomerular capillaries, pulmonary capillaries*, or both, with deposition of anti-GBM autoantibodies. Lung involvement causes pulmonary haemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents
Large vessels	
Takayasu arteritis (TAK)	Arteritis, often granulomatous, predominantly affecting the aorta and/or its major branches. It can affect the *pulmonary arteries* causing pulmonary hypertension. Onset usually in patients younger than 40 years
Variable vessel	
Behcet's disease (BD)	Vasculitis occurring in patients with Behcet's disease that can affect arteries or veins. Behcet's disease is characterized by recurrent oral and/or genital aphthous ulcers accompanied by cutaneous, ocular, articular, gastrointestinal, and/or central nervous system inflammatory lesions. Small vessel vasculitis, thromboangiitis, *thrombosis*, arteritis, and *arterial aneurysms* may occur

Adapted from Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65(1):1–11

2012 [2]. Histological descriptive terms were used to replace eponyms. The principle pulmonary vasculitides are associated with anti-neutrophilic cytoplasmic antibody (ANCA) and called the ANCA-associated vasculitides (AAV). These consist primarily of granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss Syndrome) and microscopic polyangiitis (MPA).

Epidemiology

The prevalence of vasculitis is estimated to be between 90 and 278 per million, depending on whether clinic- or population-based surveys are utilised, the latter giving rise to the higher value. The annual incidence of vasculitis is estimated at 11–20 per million. Although the incidence of AAV is similar across Europe, there is an increased incidence of GPA and EGPA in northern Europe and increased incidence of MPA in southern Europe. There is a seasonal and cyclical incidence of GPA, with it being more common in the winter and seeming to have a peak incidence every 3–4 years.

Aetiology

The precise aetiology of the ANCA-associated vasculitides is unknown. Infections (commonly *S. aureus*, *E. coli* and *Klebsiella*) have

been implicated in GPA. Chronic carriers of *S. aureus* who express toxic shock toxin 1 have an increased frequency of relapses. Molecular mimicry between bacterial antigens and ANCA (*E. coli, S. aureus*), toll-like receptor activation (*S. aureus*) and idiotype-anti idiotype mechanism with bacterial antigens (*S. aureus* and *Klebsiella*) have been shown to be associated with ANCA-associated vasculitis.

A genome-wide association study found anti-proteinase 3 ANCA (PR3 ANCA) was associated with HLA-DP and the genes encoding α_1-antitrypsin (SERPINA1) and proteinase 3 (PRTN3). This supported the clinical observation that patients with ZZ α_1-antitrypsin deficiency have a 100-fold increased risk of developing GPA. Anti-myeloperoxidase ANCA (MPO ANCA) is associated with HLA-DQ.

Occupational exposure to silica, quartz, organic solvents, arable crops, and livestock farming has been associated with AAV. In addition, drugs which have been linked with the development of AAV include propylthiouracil, hydralazine, carbimazole, D-pencillamine, phenytoin, allopurinol, and sulphonamides.

Pathogenesis

The pathogenesis of MPA is now well understood. In murine *in vivo* studies MPO ANCA has been shown to be pathogenic. When MPO-deficient mice were immunized against MPO and their splenocytes or IgG were transferred to normal recipient mice, the recipients went on to develop pulmonary capillaritis and glomerulonephritis, which was histologically identical to MPA.

Further evidence to support the pathogenicity of MPO ANCA in the development of MPA comes from the clinical observation that a pregnant woman with active MPO-ANCA positive MPA gave birth to a child with pulmonary haemorrhage and glomerulonephritis. The neonate's blood contained IgG MPO ANCA, and it was presumed that passive placental transfer of maternal IgG MPO ANCA caused the disease.

Clinical Approach to Patients with Suspected AAV

The presentation of vasculitis can be variable, making early diagnosis and treatment a challenge. There are no accepted specific diagnostic criteria for vasculitis, but there are classification criteria aimed at differentiating them from each other, as seen in Table 17.2. There is frequently a history of prodromal symptoms of fevers, malaise, night sweats, flitting arthritis, weight loss, headache, and polymyalgia in the preceding 6 months. The main pulmonary vasculitides are reviewed below, and recommended investigations are listed in Table 17.3.

Table 17.3 Investigations for vasculitis

Investigation for vasculitis[a]	
All patients	
Blood tests	FBC, U&E, CRP
Urine dipstick and microscopy	
CXR	
Selected tests depending on presentation	
Blood tests	ANCA
	Blood culture
	Hepatitis B and C
	HIV
	Anti-GBM
	Rheumatoid factor, ANA, anti-phosholipid antibody
	Cryoglobulin and complement
Radiology	HRCT thorax
Pulmonary physiology	Spirometry with flow volume loop
Bronchoscopy	To exclude infection and confirm alveolar haemorrhage; rarely mucosal biopsy and transbronchial biopsies are useful
Biopsy of relevant tissue	Kidney, lung, or nasal
Neurological	Nerve conduction test
Cardiology	Echocardiogram

[a]Full blood count (FBC) looking for neutrophilia, eosinophilia, or a drop in haemoglobin, together with urea and electrolytes (U&E) looking for renal damage, should be routinely undertaken. Vasculitis is found with infections, and blood cultures to exclude bacteraemia (especially due to sub-acute endocarditis) should be considered. Mixed cryoglobulinaemia is invariably found with hepatitis C. Auto-antibody screen to exclude other connective tissue diseases should be carried out if indicated

Table 17.4 The main imitators of vasculitis

Infections	
Acute	Mycotic aneurysms associated with septicaemia, sub-acute endocarditis
Chronic	TB, HIV, syphilis, hepatitis
Malignancy	Haematological—lymphoma, myeloma, leukaemia
	Atrial myxoma
Hypercoaguable states	Anti-phospholipid syndrome
	Thrombotic thrombocytopenic purpura
Hereditary	Ehler-Danlos
	Marfan's
Other	Cocaine abuse
	Cholesterol emboli

It is important to exclude infection and other mimics of vasculitis because treatment of vasculitis entails the use of immunosuppressive drugs, and the consequences of not recognising infection may be devastating. The main mimics of vasculitis are listed in Table 17.4.

Granulomatosis with Polyangiitis (Wegener's)

Granulomatosis with polyangiitis (GPA) is classically characterised by the triad of upper respiratory tract, lower respiratory tract, and renal involvement. However, up to 25% of patients will have a limited form of GPA, with only upper and lower respiratory tract involvement. Tissue damage is characterised by necrotizing granulomatous inflammation affecting predominantly small to medium vessels.

It is a disease which predominantly occurs in the third to the fifth decade of life. It is rare in children. A second peak of incidence is found with increasing age. GPA has a prevalence of 24–145 per million, with an annual incidence of 8.4 per million population.

Clinical Features: Upper Airways

GPA invariably involves the upper airways. Ear, nose, and throat symptoms are the most common symptoms at initial presentation, and are present in over 90% of patients during their disease history. Rhinosinusitis associated with epistaxis and nasal crusting is present in 70% of patients at initial presentation. Hearing loss will develop in 15–25% of patients, due to inflammation of either the middle ear or Eustachian tube. Nasal disease can progress to nasal septal perforation, and saddle nose deformity due to vascular necrosis of cartilage. Nasal crustation can cause impaired nasal breathing and chronic cough.

Clinical Features: Lower Airways

Granulomatous involvement of the trachea and bronchi can lead to stenosis in 10–30% of patients. This is more common in female patients. Subglottic narrowing is the most common site of involvement, and is invariably associated with active nasopharyngeal disease. Symptoms arising from airway narrowing are variable and may include exertional dyspnoea, "wheeze," change in voice, haemoptysis, and persistent cough. At the time of bronchoscopy only 26% of airway narrowing is due to acute inflammation, with fibrous mature scarring as the predominant cause of the narrowing.

Lung parenchymal involvement may present with cough, haemoptysis, or recurrent infective symptoms, or may be silent. Radiographic abnormalities are noted in more than 70% of patients at some point during their disease. These range from single to multiple lung nodules found in 20–50% of patients. Cavitation of lung nodules will occur in two-thirds of cases. Pulmonary infiltrates, consolidation, intrathoracic lymphadenopathy, atelectasis, pleural thickening, and pleural effusions have all been described (Fig. 17.1a–d).

Extrapulmonary Features

Renal presentation of disease can be insidious. Microscopic haematuria is frequently overlooked, and a dipstick examination of the urine for

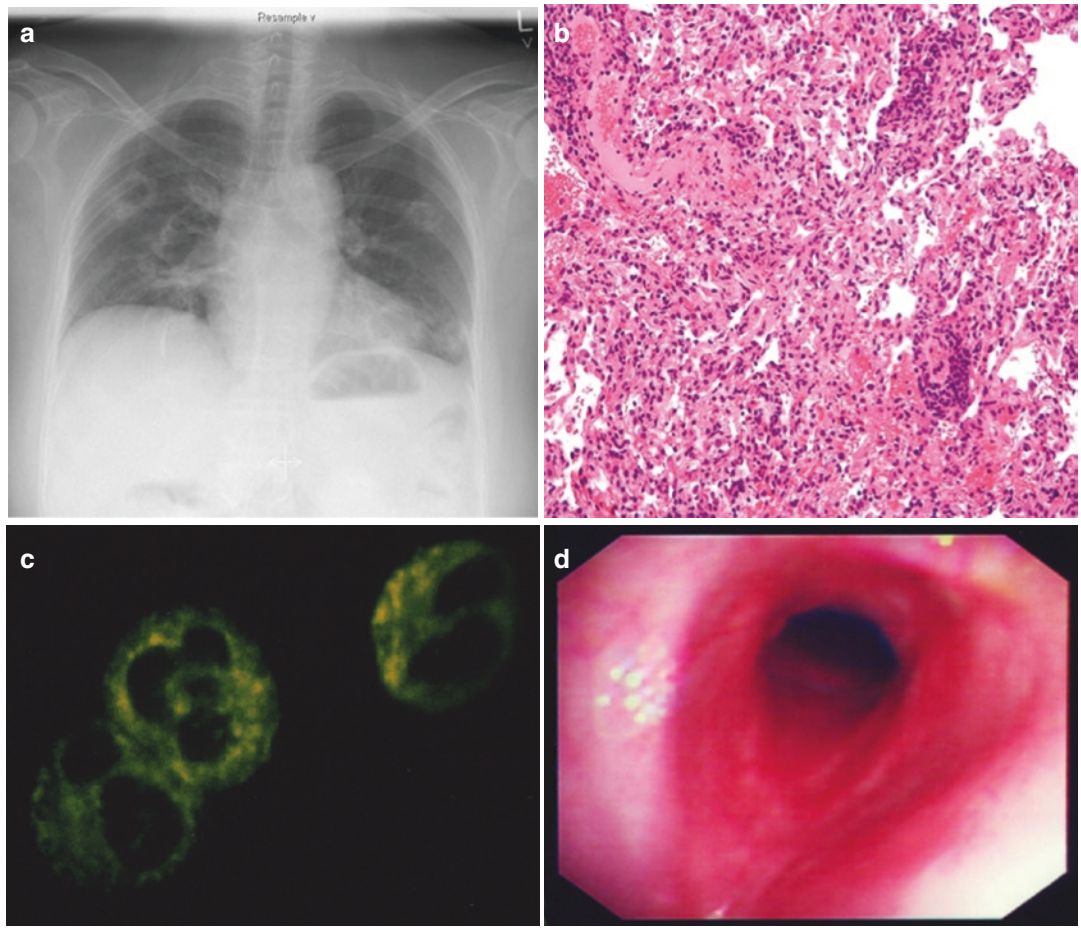

Fig. 17.1 (**a**–**d**) Granulomatosis with polyangiitis. (**a**) A chest radiograph in a patient with multiple lung nodules with both cavitatory and solid appearance. (**b**) CT guided biopsy undertaken due to concern of metastatic carcinoma shows small and medium vessel vasculitis with necrosis with the giant cells. (**c**) Immunofluoresence shows C-ANCA staining pattern with cytoplasmic staining. (**d**) Subglottic stenosis is shown with involvement of the vocal cords inferiorly

blood and protein should always be undertaken. Involvement of the eye may present with visual disturbance, pain, grittiness, and dryness in up to 30% of patients. Granulomatous inflammation of the orbits can cause proptosis in up to 15% of patients. Conjunctivitis, episcleritis, and scleritis may also occur.

Palpable purpura, skin ulcers, and haemorrhagic lesions have all been described as dermatological presentations. Neurological, cardiac, and gastroenterological presentations with mononeuritis multiplex, heart failure or arrhythmias, and gastrointestinal bleeding, respectively may occur in GPA, but are less common than in EGPA.

Microscopic Polyangiitis (MPA)

MPA is characterised by a necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis frequently occurs. Although some of its features overlap with GPA, it is distinguished by the absence of granulomatous inflammation and lack of upper respiratory tract involvement. In its most severe manifestation it is a cause of pulmonary-renal syndrome.

It is more common in men and is typically but not invariably associated with ANCA positivity. It

has a peak incidence in the sixth decade. It has a prevalence of six to seven per million, and an annual incidence of one per million in Northern Europe.

Clinical Features

There is typically a prodromal illness with fever, weight loss, arthralgia, myalgia, and fatigue that precedes the diagnosis. Pulmonary involvement includes diffuse alveolar hemorrhage, pleurisy, and pleural effusions. Presenting symptoms are dyspnea, cough, or hemoptysis, and can occur in up to 30% of patients. Recurrent and chronic sub-clinical alveolar haemorrhage has been associated with pulmonary fibrosis, and carries a poor prognosis.

Renal involvement is present in over 90% of patients. Crescentic glomerulonephritis and focal segmental glomerulonephritis with fibrinoid necrosis are typically seen. Microscopic haematuria with proteinuria is commonly found.

Gastro-intestinal involvement has been reported in 30–40% of patients. It can present with abdominal pain, diarrhoea, ischaemia, or bowel perforation. Neurological (mononeuritis multiplex, cerebral vasculitis); dermatological (leukocytoclastic vasculitis); musculoskeletal (arthritis); ophthalmic (retinal vasculitis); and cardiological (myocarditis and pericarditis) involvement have all been described.

Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss Syndrome)

Eosinophilic granulomatosis with polyangiitis (EGPA) is characterised by eosinophil-rich and necrotizing granulomatous inflammation, often involving the respiratory tract, associated with asthma. It has a prevalence of 10–13 per million in Northern Europe. In asthma sufferers it has a significantly higher prevalence of 67 per million (1 in 15,000). There is no sex predominance for EGPA, and it can present between the ages of 15 and 75, with a median age of presentation of 50.

The diagnosis of EGPA poses a challenge due to overlap with hypereosinophilic syndromes. The European Respiratory Society has proposed the following for the diagnosis of EGPA:

- Asthma (with or without pulmonary opacities)
- Blood eosinophilia $>1.5 \times 10^9$ or >10% of circulating leucocytes or proven tissue eosinophilia with blood eosinophilia of $>0.75 \times 10^9$
- Vasculitis (or surrogates)
  - Necrotising vasculitis (biopsy proven of any organ)
  - Alveolar Haemorrhage (defined as bloody bronchoalveolar lavage with compatible radiology)
  - Mononeuritis multiplex
  - Necrotising glomerulonephritis
  - Palpable purpura
  - Haematuria associated with casts or haematuria and 2+ proteinuria
  - Myocardial infarction with proven coronary arteritis
  - ANCA-associated with at least one of the following
    Myocarditis or pericarditis
    Abdominal pain associated with diarrhoea
    Peripheral neuropathy

It has been noted that a subgroup of patients exists with hypereosinophilic asthma who have systemic manifestations (pericardial effusion, skin rash, neuropathy) without evidence of vasculitis and who are ANCA negative. Longitudinally over time these patients may go on to develop a vasculitis. The term "hypereosinophilic asthma with systemic manifestation" has been coined to describe them.

Clinical Features

Three phases in the development of EGPA have been suggested. A *prodromal phase* in which asthma (including cough-variant asthma) has been present for several years. This phase is often associated with rhinosinusitis and nasal polyposis. This is followed by an *eosinophilic phase* in which there is a peripheral eosinophilia with tissue infiltration which can be initially labelled simple pulmonary eosinophilia, eosinophilic

gastroenteritis, or chronic eosinophilic pneumonia. Finally, after several years, there is a *vasculitis phase* with organ involvement including (a) the nervous system, most commonly with mononeuritis multiplex; (b) the cardiac system with myocarditis, pericarditis, and coronary arteritis; (c) gastroenterological system with ischaemia and bleeding; and (d) dermatologically with subcutaneous nodules, palpable purpura, and haemorrhagic lesions.

It has been suggested that there are two types of EGPA: (1) ANCA-associated EGPA with mononeuritis multiplex, pulmonary haemorrhage, cutaneous vasculitis, and rarely renal disease; and (2) ANCA-negative EGPA with nasal polyposis, pulmonary infiltrates, cardiac disease, and eosinopilic gastroenteritis. The latter is associated with a poorer prognosis. There is, however, considerable overlap between the two.

There is a reported association of leukotriene antagonists with Churg Strauss Syndrome. Studies now suggest this is related to corticosteroid withdrawal after initiating therapy, rather than direct drug toxicity.

ANCA Patterns with AAV

ANCA testing is frequently undertaken in two steps. An initial immunofluoresence test is undertaken looking for either a cytoplasmic (C-ANCA) or peri-nuclear staining pattern (P-ANCA). Then, if positive, an enzyme-linked immunosorbent assay (ELISA) is undertaken. The primary antigen in C-ANCA is the serine protease 3, PR3-ANCA, and in P-ANCA is myeloperoxidase, MPO-ANCA. In addition, other C-ANCA and P-ANCA antigens, including antibodies to bacterial permeability inhibitor (BPI) associated with cystic fibrosis and h-LAMP-2 (associated with necrotising glomerulonephritis), have been described.

Patients with GPA have a positive ANCA in up to 96% of cases, with 88% being PR3 ANCA positive. In contrast, patients with MPA have a positive ANCA in up to 98% of cases, with 79% being MPO-ANCA positive. In the case of EGPA, up to 64% of patients will be ANCA positive, with MPO-ANCA accounting for the majority of cases.

ANCA-positive ELISA results can be found incidentally, but may herald the development of vasculitis. A period of observation is recommended in patients with positive results without evidence of vasculitis.

Medical Management and Treatment of AAV

Until the advent of cyclophosphamide and corticosteroid therapy, vasculitis carried a poor prognosis, with 90% 2-year mortality in the 1960s. In the subsequent years a series of pivotal clinical studies altered the management and prognosis of vasculitis. These studies and the staging criteria of the disease proposed by the European vasculitis study group (EUVAS) have helped develop guidelines on the management of vasculitis. The staging criteria are:

- *Limited disease*. Disease confined to the upper airways that is usually applied to GPA.
- *Early generalised disease*. This signifies disease without threatened end organ function. Nodular and cavitatory lung disease fall into this category.
- *Active generalised disease*. This denotes disease with threatened end organ function. This is usually applied to threatened renal damage.
- *Severe disease*. This signifies impending end organ failure and dysfunction. Examples include diffuse alveolar haemorrhage and severe renal failure
- *Refractory disease*. Disease that has failed to enter remission despite appropriate therapy.

The European League Against Rheumatism (EULAR) in 2009 and the British Rheumatology Society (BSR) in 2013 published guidelines on the management of small- to medium-vessel vasculitis and large-vessel vasculitis [3–5]. Their recommendations for the management of small- to medium-vessel vasculitis have been modified in Table 17.5. The key recommendations are:

Table 17.5 Treatment of AAV based on site and severity of disease

Clinical class	Localised	Early systemic	Generalised systemic	Severe	Refractory
Constitutional symptoms	–	+	+	+	+
Renal function	Creatinine <120 µmol/L	Creatinine <120 µmol/L	Creatinine <500 µmol/L	Creatinine >500 µmol/L	Any
Threatened organ function	–	–	–	+	+
Induction	Single agent (CS, AZA, MXT)	CYC + CS or MTX + CS	CYC + CS or CS+ RTX	CYC+ CS+ PE	CYC + CS + PE ± RTX
Recommended dosage	CS (1 mg/kg/day) tapered down to 0.25 mg/kg/day by 12 weeks				
	AZA 1–2 mg/kg/day				
	MTX 20–25 mg/week				
	Oral CYC 1.5–2 mg/kg/day				
	PE seven exchanges within first 2 weeks				
	RTX 2× 1 g infusion 2–4 weeks apart with six monthly repeat				
Maintenance	Once remission is achieved with CYC or RTX transition to maintenance with AZA 1–2 mg/kg or MTX 20–25 mg/week should be considered The duration of maintenance therapy should be 12–24 months				

CS Corticosteroid, *AZA* Azathioprine, *MTX* methotrexate, *CYC* Cyclophosphamide, *PE* Plasma exchange, *RTX* Rituximab

- That patients with primary small- and medium-vessel vasculitis should be managed in collaboration with, or at, centres of expertise.
- ANCA testing (including indirect immunofluorescence and ELISA) should only be performed in the appropriate clinical context.
- A positive biopsy is strongly supportive of vasculitis, and it is recommended that the procedure is used to assist diagnosis and further evaluation for patients suspected of having vasculitis. These include CT-guided lung biopsy or open lung biopsy if the diagnosis cannot be made from tissue elsewhere.
- The use of a structured clinical assessment, urine analysis, and other basic laboratory tests at each clinical visit for patients with vasculitis is recommended.
- Patients with ANCA-associated vasculitis should be categorised according to different levels of severity to assist treatment decisions.
- It is recommended that a combination of cyclophosphamide (intravenous or oral) and glucocorticoids or rituximab and corticosteroids (if cyclophosphamide is contraindicated) is used for remission induction in generalised primary small- and medium-vessel vasculitis.
- It is recommended that a combination of methotrexate and glucocorticoid (as a less toxic alternative to cyclophosphamide) is used for the induction of remission in non-organ threatening or non-life threatening ANCA-associated vasculitis.
- Assessment for *Staphylococcus aureus* nasal carriage should be carried out and if detected, eradication therapy with nasal mupirocin should be carried out.

Predictors of Relapse in Treatment of AAV

Studies have shown that the risk factors for relapse in AAV include (a) a diagnosis of GPA; (b) ENT disease; (c) PR3 ANCA; (d) persistent ANCA despite treatment; (e) an increase in ANCA titres; (f) immunosuppression reduction (i.e. azathioprine, methotrexate or mycophenolate withdrawal); (g) lower total cyclophosphamide exposure; and (h) corticosteroid withdrawal.

Detection and Protection Against Adverse Effects of Treatment

Mesna Treatment for Oral Cyclophosphamide

Epidemiological studies have shown the cumulative dose of cyclophosphamide (>30 g) is associated with uroepithelial carcinoma. Mesna protects by scavenging the urotoxic acrolein metabolite of cyclophosphamide. Patients who are smokers can develop uroepithelial toxicity at a lower cumulative dose than non-smokers, and should therefore be screened for non-vasculitis-related haematuria.

Pneumocystis jirovecii Prophylaxis Treatment

Early studies have shown the risk of *Pneumocystis jirovecii* pneumonia can be as high as 20%. This is more frequently observed when high-dose corticosteroids therapy is used. It is recommended that trimethoprim/sulphamethoxazole be used either as 960 mg alternate days or 480 mg od. At this low dose it appears safe to use in conjunction with methotrexate, but it is advised to omit prophylaxis on the day that methotrexate is taken because of concerns about myelotoxicity.

Immunoglobulin Level Monitoring for Patients on Rituximab

Rituximab therapy leads to B lymphocyte depletion and secondary hypogammaglobulinaemia. Immunoglobulin levels and lymphocyte subclasses should be checked prior to each therapy with rituximab. If recurrent infections and hypogammaglobulinaemia occur, immunoglobulin replacement therapy should be considered.

Prognosis of AAV

The prognosis of AAV prior to corticosteroids and cyclophosphamide was a 1-year mortality of 80% and 2-year mortality of 90%. These figures have now reversed, with over 90% of patients

now achieving remission. A study following up 535 patients with newly diagnosed GPA or MPA entered into EUVAS clinic trials found an increased mortality ratio of 2.6 compared to the general population. Survival at 1 year, 3 years, and 5 years was 88%, 85%, and 78% respectively. Predictors of poor survival at presentation were advanced renal failure, increasing age, a high Birmingham vasculitis assessment score (BVAS), high white blood cell (WBC) count, and a low haemoglobin.

In a separate study, the French Vasculitis Study Group reviewed the data of 1108 patients in their database. They reported a 5-year survival of 72.5% (MPA), 86.1% (EGPA), and 86.9% (GPA). They described a five factor score where each of the following scored 1 point (1) age > 65 years; (2) cardiac symptoms; (3) gastrointestinal involvement; (4) renal insufficiency with a stabilized creatinine >150 μmol/L; and (5) the absence of ENT symptoms, which are protective in GPA and EGPA. Scores of 0, 1, and ≥2 were associated with 5-year survival of 91%, 79%, and 60% respectively.

Other Pulmonary Vasculitides

Behçet's Disease

Behçet's disease is a rare multisystem disease characterised by vasculitis affecting variable sized arteries and veins [6]. It is associated with the clinical triad of recurrent oral ulceration, recurrent genital ulceration, and uveitis. It is seen more commonly in men of Mediterranean and Middle Eastern origin. The highest prevalence is in Turkey, where there is a prevalence of 100 per million population. There is an association with HLA-B51 (in 50–70% of patients) and GIMAP (GTPase immune-associated proteins) family of proteins, indicating genetic factors in its aetiology. The mechanism of the pathogenesis of the disease remains unclear.

Clinical Features

Diagnosis is made when oral ulceration together with two of the following four criteria are present: (1) cutaneous lesions; (2) genital ulceration; (3) ocular lesions (retinitis or uveitis); and (4) pathergy (an exaggerated erythematous papular response to a small needlestick).

Pulmonary manifestations frequently found include pulmonary artery aneurysms, pulmonary artery thrombosis, pulmonary infarction, consolidation, mosaic perfusion, pleural effusions, and pleural nodules. There is a rarer pulmonary variant of Behçet's disease called Hughes Stovin syndrome, which is characterised by multiple pulmonary aneurysms, peripheral venous thrombosis, recurrent fever, haemoptysis, and cough, without oral and genital ulceration.

Radiological Investigations

The most common finding on chest radiographic and CT findings are lung masses attributed to a pulmonary artery aneurysm (Fig. 17.2). After the aorta, the pulmonary artery is the second most common site of large vessel arterial involvement. In Behçet's disease, pulmonary artery aneurysms are more common than thromboembolic disease. Pulmonary artery aneurysms can regress after medical treatment with steroid and/or immunosuppressive agents.

Treatment

There are no randomised large population-based clinical trials to provide evidence for pulmonary disease treatment recommendations in this rare disease. The presence of pulmonary artery aneurysms requires a combination of cyclophosphamide and corticosteroids. The aneurysms frequently regress with the use of steroids. There are case reports where aneurysms associated with recurrent bleeding have been managed with embolization.

Takayasu's Arteritis

Takayasu's arteritis is a rare, often granulomatous, large-vessel vasculitis, predominantly

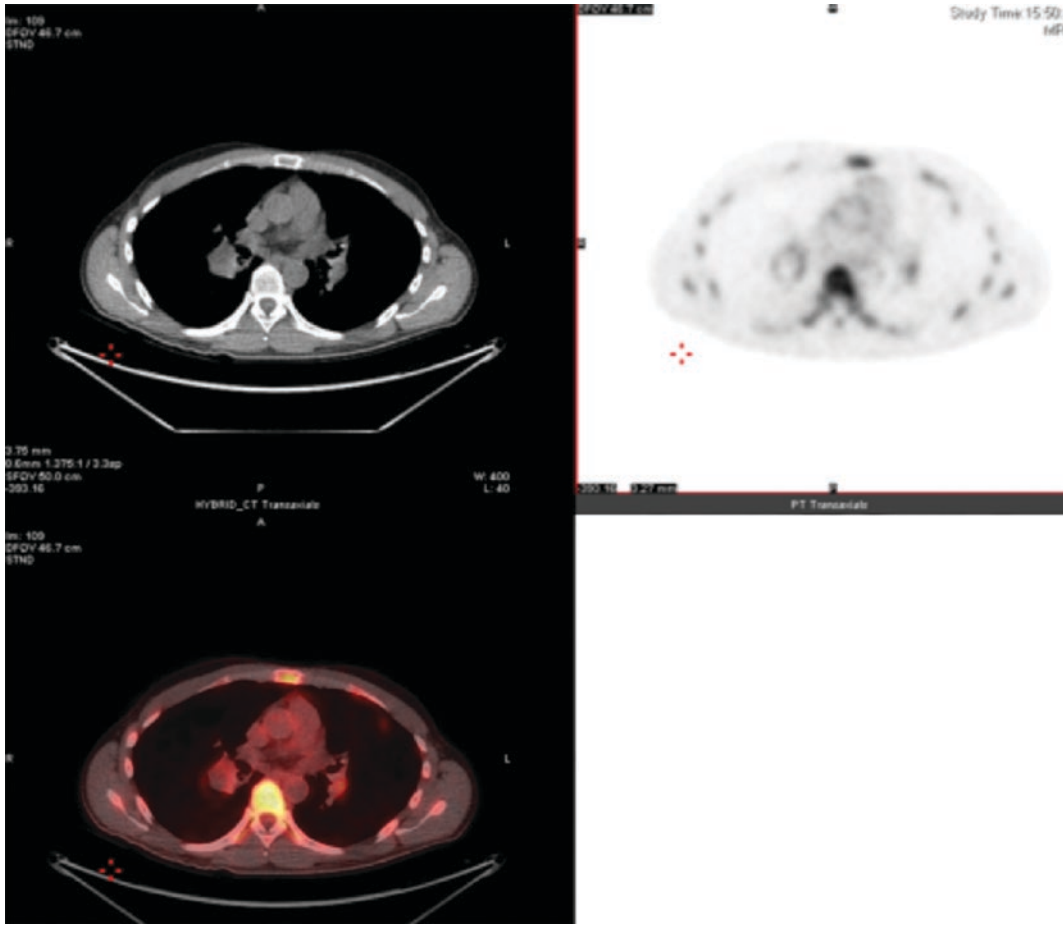

Fig. 17.2 A CT-PET showing large vessel saccular aneurysm of the right pulmonary artery with uptake of FDG, typically seen in Behcet's disease. These aneurysms will regress with therapy. Although tissue confirmation is rarely feasible in life, post-mortem samples show both vasculitis and thrombosis in the wall and lumen of the vessels

affecting the aorta and/or its major branches. It can sometimes affect the pulmonary arteries, causing pulmonary hypertension. Onset usually occurs in patients younger than 40 years. It is more common in females.

Clinical Features

Non-specific constitutional symptoms, such as fever, weight loss, arthralgias, myalgias, and malaise, together with exertional dyspnea (75% of patients), haemoptysis (42% of patients), palpitations and chest pain (49% of patients), can occur. Physical examination is usually unhelpful, but absent or diminished pulses and discrepancy in blood pressures have been noted in 49% of patients.

Radiological Investigations

Histological diagnosis of pulmonary artery Takayasu's disease is unusual, and a clinico-radiological diagnosis is usually made. The radiological features seen on CT, magnetic resonance imaging, and pulmonary angiography include irregularity, narrowing, and occlusion of the pulmonary arteries. CT-PET and dual-energy CT can show increased uptake in the walls of the pulmonary arteries, reflecting active granulomatous inflammation.

Treatment

As with Behçet's disease, there are no large, randomised clinical trials on which to base treatment recommendations. The majority of patients respond to oral corticosteroids and steroid-sparing agents such as methotrexate or azathioprine. In resistant disease cyclophosphamide and anti-TNF therapy have been used. There are case reports of refractory vessel stenosis disease being treated with balloon angioplasty and stenting.

Autoimmune Diseases

Anti-Glomerular Basement Membrane (Anti-GBM) Disease (Goodpasture's Disease)

This rare disease is characterized by the association of pulmonary haemorrhage, extracapillary glomerulonephritis, and anti-glomerular basement membrane antibodies [7]. It was first described in 1919 by Ernest Goodpasture, who reported pulmonary haemorrhage and rapidly progressive glomerulonephritis in an 18-year-old patient with 'flu.

The annual incidence in Northern Europe is estimated at 1 per million. The age of onset is associated with two peaks, the first one in the third decade of life, and a further smaller peak in the sixth to seventh decade of life. There is a seasonal incidence of anti-GBM, with it being more common in the spring and early summer. Mechanical damage to the kidney by lithotripsy and ureteric obstruction has been associated with development of anti-GBM disease.

Alveolar haemorrhage occurs predominantly in younger men. In the older peak, isolated renal disease is more common with no sex predominance. Alveolar haemorrhage is invariably associated with cigarette smoking or exposure to inhaled hydrocarbons. Pulmonary haemorrhage in the absence of renal disease is rare. An overlap syndrome between ANCA vasculitis and anti-GBM disease has been described. Up to 32% of patients who test positive for anti-GBM antibodies will also test positive for ANCA. MPO-ANCA is the most frequently associated is this scenario.

Pathogenesis

Evidence for the role of anti-GBM antibodies in the development of Goodpasture's disease came from the classical adoptive transfer experiments. Antibodies from humans with Goodpasture's disease were transferred to monkeys, which developed glomerulonephritis and alveolar haemorrhage with antibodies binding to the glomerular basement membrane. Additional evidence came from patients undergoing renal transplantation for Goodpasture's disease. Those who still had circulating antibodies present at the time of transplantation went on to develop disease in the donor kidney. Furthermore, antibody removal by plasmapheresis is associated with recovery from alveolar haemorrhage and renal failure.

The basement membrane is an extracellular structure composed primarily of collagen, laminin, and proteogylcans. Type IV collagen forms a matrix on which other components integrate. Type IV collagen comprises three sub units: α3, α4, and α5, assembled into a monomer. These monomers are then joined at their non-collagen C terminal domain (NC1) via disulphide bridges to form hexamers. Studies have shown anti-GBM antibodies are directed against Type IV collagen, and specifically the NC1 domain of α3 chain [8].

In addition to evidence for antibody-mediated disease, there is evidence showing auto-reactive T cells play a part in the development of disease. Anti-GBM disease has a positive association with the human leukocyte antigen HLA-DR15 haplotype, particularly the DRB1*1501 allele, and negative associations with HLA-DR1 and DR7, which are viewed as protective.

Anti-GBM antibodies are frequently found in the general population in low titres. The difference between healthy normal individuals and those with anti-GBM disease is that the antibodies are restricted to IgG2 and IgG4 in healthy individuals, compared to IgG1 and IgG3 in patients with anti-GBM disease. It is thought that the ability of different subclasses to bind to

Fc receptors is implicated in the pathogenesis of disease with IgG1 and IgG3.

Clinical Features

Patients frequently have a prodromal constitutional systemic illness similar to that seen in vasculitis, with symptoms of fever, sweats, loss of appetite, and arthralgia. They may suffer dyspnoea in the absence of alveolar haemorrhage due to anaemia.

Pulmonary haemorrhage presenting with haemoptysis has historically been the predominant symptom associated with disease. This is now changing with the reduction of smoking, especially among young men. It usually heralds renal involvement in the ensuing months. Infections are frequently associated with the onset of anti-GBM disease as in the original description with influenza.

Renal disease can occur in isolation (more commonly in the older peak incidence) or in conjunction with pulmonary haemorrhage. It is usually rapid in evolution. Initially microscopic haematuria with casts is present and it can progress rarely in severe disease to macroscopic haematuria. Patients may present with oliguria or anuria with volume overload and symptoms of uraemia.

Investigations

Radiology

The chest radiograph is abnormal in up to 80% of patients. It classically shows central diffuse infiltrative shadowing with peripheral sparing. In addition, ill-defined nodules and consolidative changes have been reported. CT findings mirror that of the chest radiograph, with perihilar ground glass changes with peripheral sparing (Fig. 17.3a–d).

Pulmonary Function Testing

An increase in K_{CO} (corrected gas transfer coefficient) is described as the most sensitive and specific test for alveolar haemorrhage. The mechanism for this is that the free haemoglobin in the alveoli is able to bind inspired carbon monoxide and increase K_{CO} values.

Serology and Tissue Biopsy

The presence of circulating anti-GBM antibodies and tissue biopsy evidence of anti-GBM antibodies fixed to glomerular or alveolar basement membrane is used to make a diagnosis.

Differential Diagnosis for Pulmonary Renal Syndrome

The main causes of pulmonary renal syndromes are the vasculitides, especially MPA. There is overlap between MPA and anti-GBM disease. In this setting, antibodies to both ANCA (mainly MPO) and anti-GBM are found simultaneously. Patients tend to have lower levels of anti-GBM antibodies and are managed as MPA vasculitis. Other causes of pulmonary renal syndrome are listed in Table 17.6.

Treatment of Anti-GBM Disease

Unlike the pulmonary vasculitides, there are no large randomised trials upon which to base treatment decisions. The treatment of choice is corticosteroids (1 mg/kg/day), cyclophosphamide (2 mg/kg/day), and plasmapheresis (daily 4 L plasma exchange with 5% albumin for 14 days or until anti-GBM antibodies are undetectable). Smoking cessation in smokers is encouraged.

Prognosis

In contrast to pulmonary vasculitides, relapse is rare in anti-GBM disease. When relapse does occur, it may be related to the development of overlap disease with AAV. Predictors for mortality are high anti-GBM antibody titres and the presence of ANCA. Predictors of kidney survival are the serum creatinine on presentation, the need for dialysis, and the percentage of crescents seen on renal biopsy.

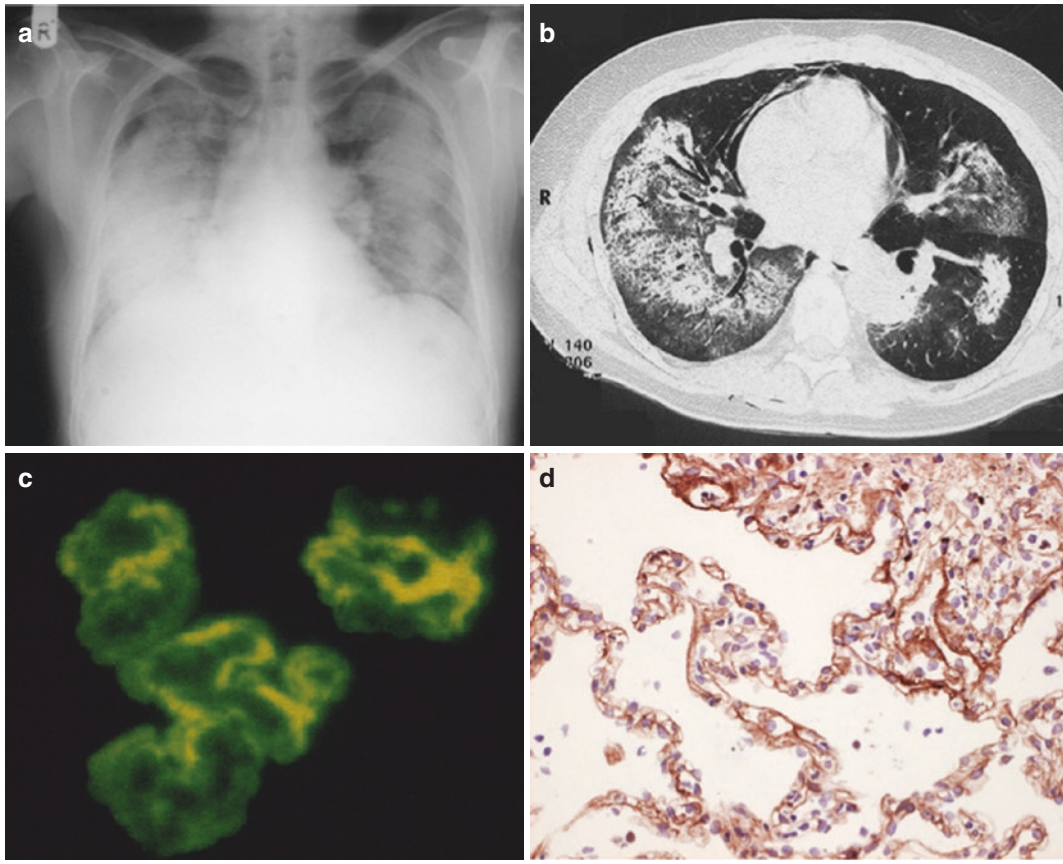

Fig. 17.3 (**a**–**c**) A case of diffuse alveolar haemorrhage due to Anti-glomerular basement membrane (GBM) disease with overlap with microscopic polyangiitis. (**a**) Shows a typical chest radiograph with peripheral sparing of the lung fields. (**b**) A CT confirms with perihilar ground glass changes with peripheral sparing. (**c**) Immunofluoresence shows P-ANCA staining pattern with peri-nuclear staining. ELISA showed this was due to antibodies to myeloperoxidase (MPO). (**d**) Lung biopsy shows alveolar basement membrane staining brown showing the presence of anti-GBM antibodies

Table 17.6 The differential diagnosis of pulmonary renal syndrome

Pulmonary vasculitides	Microscopic polyangiitis[a]
	Granulomatosis with polyangiitis[a]
	Eosinophilic granulomatosis with polyangiitis[a]
	Behcets disease[a]
	Henoch Schonlein[a]
Secondary vasculitis	Systemic lupus erythematosus[a]
	Anti-glomerular basement membrane disease[a]
	Polymyositis[a]
	Rheumatoid arthritis[a]
	Drug induced vasculitis
	Post infective (pneumonia with glomerulonephritis)
Other causes	Paraquat poisoning
	Renal thrombosis with pulmonary emboli
	Pulmonary oedema with renal failure

[a]Associated with a rapidly progressive glomerulonephritis

Pulmonary Alveolar Proteinosis

Pulmonary alveolar proteinosis (PAP) is a rare lung disease, with an annual incidence of 0.2 cases per million. It is characterised by the accumulation of lipoproteinaceous material within the alveoli due to impaired surfactant clearance by macrophages [9].

There are three main types of PAP: (1) Primary autoimmune PAP; (2) secondary PAP related to various conditions including haematological malignancy, infection, and inhalation of hydrocarbons or mineral dusts; and (3) inherited genetic. The following section will concentrate on autoimmune PAP.

Pathogenesis

The serendipitous finding that knockout mice deficient in granulocyte monocyte colony stimulating factor (GMSCF) developed a disease process histologically similar to PAP has been the basis of understanding the mechanism of disease in PAP.

Type II pneumocytes secrete surfactant proteins (A, B, C, and D) and lipids into the alveoli. Surfactant reduces alveolar surface tension and prevents alveolar collapse at the end of expiration. Alveolar macrophages play a pivotal role in the clearance of surfactant proteins and lipids. GMCSF controls the migration, differentiation, and function of alveolar macrophages. In primary auto-immune PAP there are high concentrations of neutralising anti-GMCSF IgG antibodies. These antibodies bind GMCSF, preventing macrophage clearance of surfactant, and reduce their anti-infection abilities. Anti-GMCSF antibodies have been shown to be pathogenic in adoptive transfer experiments.

Clinical Presentation

The presentation of PAP is non-specific, with dyspnoea and cough being the most common symptoms. The presence of chest pain, fever, and sweats may indicate concomitant infection. Clinical examination may reveal cyanosis, clubbing, and crepitations on auscultation.

Investigations

Radiology

The characteristic chest radiograph in PAP shows diffuse symmetrical pulmonary infiltrates with sparing of the costophrenic angles and apices. Less frequently, diffuse opacities are found ranging from ground glass to reticular nodular shadowing to consolidation with air bronchograms.

The CT appearances in PAP are characteristic, showing a "crazy paving" geographical appearance. This is defined as a smooth septal line thickening superimposed on underlying ground glass changes. The extent of ground glass changes correlates with severity, as judged by pulmonary function tests and hypoxaemia (Fig. 17.4).

Although characteristic of PAP, "crazy paving" is found in a variety of other conditions including infection, malignancy, and inhalational lung injury.

Pulmonary Function Tests

Pulmonary function testing typically shows a restrictive defect with reduced diffusing capacity. There is usually desaturation on a 6-min walk, and depending on severity, resting hypoxaemia on room air.

Laboratory and Invasive Investigations

Lactate dehydrogenase is frequently elevated between two to three times the upper limit of

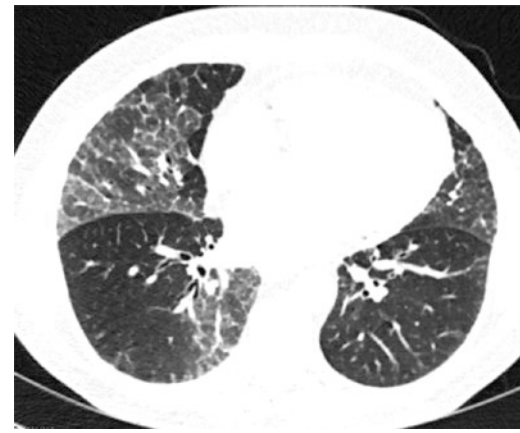

Fig. 17.4 Diffuse basal interstitial change with areas termed "crazy paving" in the right lung seen in a case of pulmonary alveolar proteinosis (PAP)

normal. It has been suggested that it may be a useful to monitor disease control in PAP. Anti-GMCSF antibodies are found in autoimmune PAP. In addition, anti-GMCSF antibodies have been described in acute myeloid leukaemia and healthy normal individuals. A threshold of >19 ug/ml has been found to have a good predictive value for autoimmune PAP.

The returns from bronchoalveolar lavage (BAL) in autoimmune PAP have a macroscopically milky appearance. Cytological analysis reveals periodic acid Schiff (PAS) staining material, predominantly lymphocytic, with foamy macrophages and hyaline material. The BAL should be sent for microbiological cultures, since up to 5% of patients will also have an opportunistic infection. In the majority of cases, a combination of radiology and BAL is all that is needed to make a diagnosis. Rarely, lung biopsy in the form of transbronchial or thoracoscopic lung biopsy may be needed.

Treatment

The clinical course of autoimmune PAP is not easily predicted. In case series, up to 28% of patients have spontaneously improved.

Lung Lavage

As with other rare lung diseases, there are no large, randomised control trials on which to base treatment recommendations. Whole (or less frequently, segmental) lung lavage is undertaken in most patients except those who improve spontaneously. This is generally undertaken in an ICU or theatre setting. The patient is intubated with a double lumen endotracheal tube and paralysed. Single-lung ventilation is undertaken with a FiO2 of 1.0. The non-ventilated lung is lavaged with warm saline (37 °C) in 0.5–1.0 L aliquots. The fluid is then removed by suctioning. Sequential aliquots are instilled and removed until the return changes from milky to clear. Up to 40 L of saline may be required. Not all the lavage will be removed, and the patient will need to be ventilated for 2–3 h post-procedure for respiratory support as it is cleared. During the procedure, manual chest percussion has been used to increase the return. Although it has been reported that both lungs have been lavaged sequentially at the same sitting, our practice is to perform this on the contralateral lung 24–48 h later. There is an improvement of symptoms, pulmonary function tests, and hypoxaemia with whole-lung lavage. In over half of patients, it may be need repeating on more than one occasion.

GMCSF Therapy

Although whole-lung lavage is considered the standard of care, it is not easily available, and alternative treatments have been trialled. These include subcutaneous and inhaled GMCSF therapy. Small uncontrolled or retrospective studies have shown improvements on par with whole-lung lavage, but clinical improvement is achieved over a longer time period. A recent meta-analysis of GMCSF therapy studies showed it was only effective in 59% of patients, and so its role is unclear. One approach is to consider supplementary drug treatment following whole-lung lavage.

Rituximab and Plasmapheresis

Refractory PAP not responsive to whole-lung lavage and GMCSF have been treated on compassionate grounds with plasmapheresis and rituximab, on the basis both of these therapies would reduce circulating anti-GMCSF levels and improve disease in a similar manner to anti-GBM disease. There are small open-label studies with rituximab, which showed improvements in the primary outcome oxygenation and secondary outcomes pulmonary function and radiology. At present, rituximab and plasmapheresis cannot be recommended outside clinical trials or for refractory disease on compassionate grounds.

IgG4-Related Disease

IgG4-related sclerosing disease (IgG4-RD) is a relatively newly described condition [10]. It was initially reported in association with autoimmune

pancreatitis in the 1990s. Over the subsequent years it has been associated with biliary duct, salivary gland, renal tract, and aortic, as well as pulmonary disease. Multiorgan involvement is common with IgG4-related disease.

IgG4-RD is more common in men than women (2.8:1). It typically develops in the seventh decade of life, but has been described in patients between the ages of 15 and 75.

Pathological Findings

The diagnosis of IgG4-RD is primarily a histopathological one. It relies on the presence of elevated IgG4 positive plasma cells in tissue together with characteristic pathological features found on biopsy. These are: (a) dense lymphoplasmacytic infiltrate; (b) fibrosis, arranged at least focally in a storiform pattern (whorled matted or spoke-like appearance); and (c) obliterative phlebitis.

Other features associated with IgG4-RD include phlebitis without obliteration of the lumen, and increased tissue eosinophils. The presence of granulomas and excess neutrophils are inconsistent with a diagnosis of IgG4-RD.

A raised serum IgG4 level of >140 $mg.dl^{-1}$ is found in 70–90% of patients with IgG4-RD and 5% of the normal population, and cannot alone be used to make the diagnosis of IgG4-RD. Normal serum IgG4 levels can also be found in a minority of patients with biopsy-proven IgG4-RD.

Pathogenesis of IgG4-Related Disease

The mechanism of IgG4-RD is unclear. Evidence from studies in autoimmune pancreatitis has suggested various mechanisms. Associations with HLA DRB1*0405 and HLA DQB1*0401 indicate genetic susceptibility factors. Th2 cells and cytokines including T cytokines and transforming growth factor-β are thought to play important roles in IgG4-positive plasma cell tissue infiltration and the development of fibrosis.

Molecular mimicry has been postulated as possible mechanism. Stimulation of toll-like receptors have been shown to induce the production of IgG4, giving rise to the theory various bacteria could give rise to increased IgG4 production by stimulating the innate immune system.

Clinical Presentation of Pulmonary IgG4-RD

The symptoms of pulmonary IgG4-RD are nonspecific. They range from cough, haemoptysis, exertional dyspnoea, and chest pain through to being asymptomatic. Pulmonary disease may be an incidental finding whilst investigating disease elsewhere in up to half of patients. Constitutional symptoms (fever, sweats, and weight loss) are unusual.

Investigations

Radiology

The features found on CT include mediastinal lymphadenopathy (found >40% of all patients with Ig4-RD); solid nodular lesions occasionally with spiculations, giving concern initially of underlying malignancy; pleural thickening and nodularity (found in ~25% of patients with pulmonary disease); alveolar interstitial disease ± honeycombing; bronchiectasis; pleural effusions (rare); airway stenosis (rare); and fibrosing mediastinitis (case reports only).

Pulmonary Function Tests

Pulmonary function tests reflect the broad clinic-radiological features of disease presentation, with both restrictive and obstructive pictures found.

Laboratory and Invasive Investigations

The serum Ig4 level is raised in the majority of patients with IgG4-RD, but it is not specific or sensitive enough to make a diagnosis of disease on its own.

Bronchoalveolar lavage has been undertaken with transbronchial lung biopsy to diagnose

disease. The BAL has been shown to have a raised IgG4 levels in comparison to patients with sarcoidosis. As this correlates with raised serum levels, IgG4 measurements in lavage fluid do not help in confirming the diagnosis.

Tissue diagnosis from surgical lung biopsy, CT-guided lung or pleural biopsy, or transbronchial biopsy are key to making a diagnosis of IgG4-RD.

Differential Diagnosis

The differential diagnoses of IgG4-RD include sarcoidosis (mediastinal lymphadenopathy is common in both), malignancy (solid nodules with spiculation are found in IgG4-RD), Castleman's disease (mediastinal lymphadenopathy and masses seen with both), lymphomatoid granulomatosis and idiopathic interstitial pneumonia (similar radiological lung parenchymal disease pattern).

Treatment of IgG4-RD

In the absence of randomised clinical trial to guide the management of IgG4-RD (due to disease rarity), corticosteroid therapy in the form of prednisolone 0.5–1 mg/kg/day has emerged as the mainstay for treatment from case series involving organ threatening disease, which in the lung usually means symptomatic parenchymal or pleural disease. No specific treatment is required in non-organ threatening disease, such as lymphadenopathy alone.

The majority of patients respond well to corticosteroid therapy, but relapses are not uncommon. In this scenario there are reports of successful use of azathioprine, methotrexate, and mycophenolate in combination with corticosteroids. In refractory disease, rituximab has been used on the basis that reduction of IgG4 levels will induce remission. This has not invariably been the case. The response to treatment has been shown to be less successful in those with well-developed fibrosis.

Idiopathic Pulmonary Haemosiderosis

Pulmonary haemosiderosis is a consequence of repeated alveolar haemorrhage. Idiopathic pulmonary haemosiderosis (IPH) has to be differentiated from other causes of recurrent alveolar haemorrhage resulting in haemosiderosis. The diagnosis of IPH is made by exclusion of secondary causes, which include the imitators of vasculitis (Table 17.4) and causes of pulmonary-renal syndrome (Table 17.6). It is characterised by (a) diffuse haemorrhage within alveolar spaces; (b) haemosiderin-laden macrophages best seen with Perl's reaction with Prussian Blue stain; (c) interstitial thickening with hyperplasia of type II pneumocytes and fibrosis; and (d) the absence of capillaritis, vasculitis, granulomas, or other vascular malformations.

IPH is a rare disease, with an annual incidence of 0.2–1.0 per million [11]. Up to 20% of cases present in adult life, but the majority are children under the age of 10. In adults most cases present in the late teens to third decade of life. There is an equal sex incidence in children, and slight male preponderance in adults.

Pathogenesis

Alveolar haemorrhage is associated with dyspnoea, haemoptysis, and radiological pulmonary infiltrates. Following haemorrhage, alveolar macrophages clear the erythrocytes from the alveoli. In the process they convert haemoglobin's iron into haemosiderin within 72 h. The haemosiderin-laden macrophages stay within the lung for 4–8 weeks.

The mechanism of alveolar damage leading to IPH is unknown, and has to be differentiated from immune-mediated damage by auto-antibodies to the basement membrane in anti-GBM disease and blood vessels in ANCA-associated vasculitis, together with immune complex-mediated damage, e.g. SLE, cryoglobulinaemia, and Henoch-Schonlein purpura.

There are reports of IPH occurring in families, suggesting either a genetic or environmental cause. There is a single study linking IPH associated with coeliac disease to HLA B8*. There are associations of IPH with cow's milk allergy (Heiner's Syndrome) and coeliac disease. In these conditions, circulating immune complexes with alveolar deposition of IgA and IgG has been seen in some patients. Treatment with either milk- or gluten-free diets have resulted in improvement or remission of disease in these cases.

The role of fungal infections related to the fungus *Stachybotrys atra* and other moulds, including aspergillus and alternaria, has been postulated. It was suggested that the fungal toxin trichotecen, which inhibited angiogenesis, impaired the development of alveolar membranes in the children, causing haemorrhage. This link has been questioned in other studies.

Clinical Presentation of IPH

A triad of haemoptysis, anaemia, and pulmonary infiltrates with no other cause is described in IPH. The disease presentations can be variable, ranging from chronic development to fulminant acute disease. Symptoms include cough, haemoptysis, dyspnoea, and fatigue. Haemoptysis may be absent in children, and is invariably present in adults. Clinical examination in the acute setting may find tachypnea, pallor, tachycardia, wheeze, fever, and crackles. In chronic disease, clubbing with fibrotic crackles may develop.

Investigations

Radiology

There are no specific radiological features of IPH. Chest radiographs may show bilateral pulmonary infiltrates, which recedes and leaves reticular changes. The CT scan mirrors these changes, with diffuse infiltrative changes predominantly in the lower lobes that clear leaving a reticular-nodular pattern. Chromium isotope[51] or technetium Tc^{99} pertechnetate-labeled red cell nuclear medicine scans have been undertaken to show alveolar haemorrhage. Normal lungs do not take up red cells, but when active alveolar haemorrhage is present in IPH there is leakage and retention within the alveoli.

Pulmonary Functions Tests

In acute IPH, a raised diffusing capacity for carbon monoxide and airflow obstruction have been described. In chronic IPH, a restrictive picture with a low or normal diffusing capacity for carbon monoxide can develop.

Laboratory and Invasive Investigations

Microcytic hypochromic anaemia may be found on the full blood count. Eosinophilia and neutrophilia may be present. The ferritin level may be normal or elevated due to alveolar release from clearance of erythrocytes, and does not reflect tissue iron stores.

It is important to exclude the presence of secondary causes of pulmonary haemosiderosis. ANCA, anti-GBM antibodies, rheumatoid factor, anti-phospholipid antibody, anti-nuclear antibody, and cryoglobulins should be screened. In light of the association of IPH with coeliac disease and milk allergy, anti-gliadin antibodies together with serum precipitins to casein and lactalbumin should be performed.

Bronchoscopy and lavage is important to confirm the presence of haemosiderin-laden macrophages and exclude infection. Tissue, ideally from surgical lung biopsy, is needed for diagnosis. It allows for the exclusion of vasculitis and capillaritis as the cause of pulmonary haemosiderosis.

Treatment and Prognosis

Corticosteroids have been shown in case series to be effective. A survey of prescribing in acute and chronic IPH showed a variation of practice across the world. The mainstay in all centres was corticosteroid therapy with hydroxychloroquine, azathioprine, and cyclophosphamide used

(in descending order of use) as steroid-sparing agents. In two reported cases of lung transplantation, the disease recurred in the allograft.

The reported survival from a predominantly children-based cases series is 2–4 years from diagnosis. The prognosis in IPH for adults appears better than for children. This is thought to be related to their slower and milder disease presentation.

Cystic Lung Diseases

Cystic lung diseases have a characteristic radiological appearance on CT [12] and unlike the presence of cysts in the liver or kidneys, those in the lungs are always reflective of an underlying pathology. There are a number of causes of this phenomenon, and the main ones are listed in Table 17.7. Cysts can be differentiated from bullae or cavities, as true cysts are thin walled (less than 2–3 mm thick) and have areas of low attenuation (Fig. 17.5a–c). Bullae do not have thin walls, whereas cavities are thick-walled, gas-filled spaces which develop in areas of the lung which have consolidation, masses, or nodules. The more common appearances of cysts in the lungs include centrilobular emphysema, chronic

Table 17.7 The main causes of cystic lung disease as seen on CT scan

Centrilobular emphysema
Chronic hypersensitivity pneumonitis
Atypical infection causing pneumatocoeles
Langerhans cell histiocytosis (LCH)
Lymphoid interstitial pneumonia (LIP)
Lymphangioleiomyomatosis (LAM)
Birt Hogg Dubé syndrome
Desquamative interstitial pneumonia

Cystic appearances can be seen in centrilobular emphysema, chronic hypersensitivity pneumonitis and infection but the remainder are rarer causes of 'true cysts' in the lung. Adapted from Beddy P, Babar J, Devaraj A. A practical approach to cystic lung disease on HRCT. Insights imaging. 2011 Feb;2(1):1–7

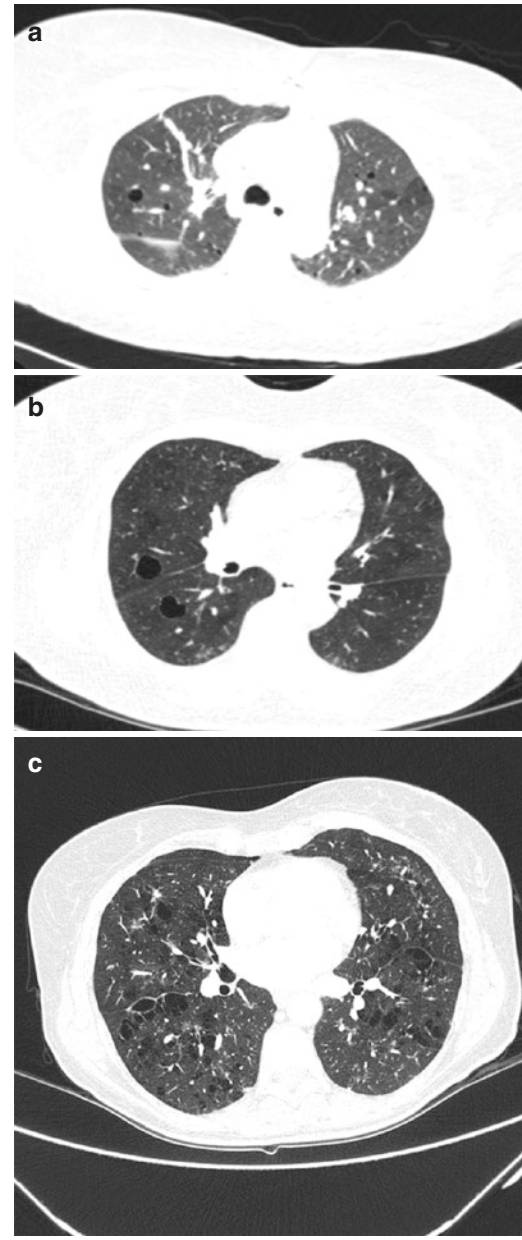

Fig.17.5 (**a**–**c**) (**a**) Scattered thin-walled cysts (up to 11 mm) in both lungs with persistent diffuse ground glass change in a case of cystic lung disease due to Birt Hogg Dubé syndrome. (**b**) Thin-walled cysts in the right lung with background ground glass and areas of extreme apical sparing due to LIP. (**c**) Scattered spiculated nodules and cysts in a patient with PLCH. There is some co-existing emphysema

hypersensitivity pneumonitis, and infections leading to pneumatocoeles. The following section covers the most important, rarer causes of "true" cystic lung disease.

Langerhans Cell Histiocytosis (LCH)

Pathogenesis

Langerhans cell histiocytosis (LCH) is a rare multisystem disorder due to the abnormal proliferation of a type of myeloid dendritic cell called a Langerhans cell [13]. The disorder is of unknown aetiology. Although a few historical studies have supported the theory of a viral aetiology, the consensus now is that the disease is a chronic inflammatory reactive condition, or even a neoplastic process. The disease can affect a number of organs including primarily the bones (causing lytic bone lesions), lymph nodes, the skin, the central nervous system, GI system, and the lungs. The multifocal form of the condition primarily affects children, with a peak incidence of 1 in 200,000 in children between 5 and 10 years old. The pulmonary form of disease occurs in approximately 10% of all cases, and this most often occurs in adults. The condition affecting the lungs has previously had a number of terms, including eosinophilic lung granulomas and histiocytosis X.

Clinical Presentation of Pulmonary LCH

Although the vast majority of cases of pulmonary LCH are associated with cigarette smoking, there is no strong evidence as to a direct cause. The condition affects both sexes equally, and most often presents between the ages of 20 and 40. Patients may present with non-specific respiratory symptoms (including cough, shortness of breath, pleuritic chest pain, haemoptysis, fever), with a spontaneous pneumothorax, with features of pulmonary hypertension in advanced disease or as an incidental finding on a CT scan.

Investigations

Chest radiographs may be non-specific, and hence the hallmark radiological test is the CT scan. The early stage of disease reveals nodules only. These progress to the classical findings of thin-walled cysts and nodules, which are found mainly in the middle and upper lobes. There may also be associated interstitial thickening. The cysts themselves have a characteristic appearance of unequal sizes and shapes. This appearance with middle and upper lobe predominance may help differentiate them from other cystic conditions. If classical, these changes seen on CT in a young smoker may be enough to make the diagnosis. If a tissue diagnosis is warranted, bronchoscopy with transbronchial lung biopsies can be performed, but this has a high false-negative rate. Surgical lung biopsy is the definitive choice and reveals a proliferation of CD1a-positive Langerhans cells.

Treatment

The mainstay of treatment is conservative, with smoking cessation crucial to improving prognosis. Supportive treatments including oxygen therapy, pulmonary rehabilitation, and treatment of pulmonary hypertension may be needed. A number of small studies have reviewed novel treatments, but none are in routine use. Glucocorticoids may help in selected cases (e.g. those with significant interstitial or nodular change), but there is no real evidence to support their widespread use in all patients. Lung transplantation may be an option in more severe cases.

Lymphangioleiomyomatosis

Pathogenesis

Pulmonary lymphangioleiomyomatosis (LAM) is a rare lung disorder of unknown cause [14]. The resulting cystic changes can be very destructive to normal lung tissue. Cyst formation is often found in conjunction with smooth muscle proliferation, and is associated with a number of extra-pulmonary features including renal angiomyolipomas, meningiomas, and cystic changes within lymph nodes.

Clinical Presentation of Pulmonary LAM

LAM predominantly affects women of childbearing age. They are more likely to be non-smokers and premenopausal. Up to 30% of patients have associated tuberous sclerosis with the findings of intellectual disability, seizures, and multiple benign soft tissue tumours. Patients predominantly present with shortness of breath, but can also present with a range of respiratory symptoms including pleuritic chest pain, cough, haemoptysis, chylothorax, and spontaneous pneumothorax.

Investigations

Chest radiographs may be normal in early disease and progress to reveal reticular nodular opacities in more advanced cases. CT scans generally reveal a large number of thin-walled cysts in both lungs which are often uniformly shaped and affect all lung fields (unlike LCH), but tend to spare the extreme apices. Bronchoscopy with transbronchial biopsy may be diagnostic in over 50% of cases, but when they are not, patients will need a surgical biopsy for a definitive diagnosis. This shows a characteristic cell morphology and protein staining.

Treatment

Treatment tends to be supportive, with supplemental oxygen, treatment of infections, management of pulmonary hypertension, and pulmonary rehabilitation. Targeted treatments have been used in a small number of patients, and the mainstay of this is the mTOR inhibitor sirolimus, which has been shown to improve a number of respiratory indicators (including 6-min walk testing, diffusion capacity, quality of life scores) but is generally reserved for patients with progressive disease due to the side effects of the drug. Lung transplantation for advanced disease may be an option.

Lymphoid Interstitial Pneumonia

Lymphoid interstitial pneumonia (LIP) is a rare benign interstitial lung disease which results from a lymphocytic infiltrate into the alveolar spaces and the lung interstitium [15]. The aetiology is unknown, but it is associated with collagen vascular disorders such as Sjogren's syndrome and other autoimmune diseases (including rheumatoid arthritis and SLE). It is also seen in patients who are HIV-positive. The condition can affect a specific part of the lung only, or become diffuse throughout both lungs. It is most often seen in middle-aged and older women, who present predominantly with shortness of breath. Respiratory examination often reveals crackles in the chest. CT scans reveal cystic changes, ground glass changes, and pulmonary nodules, but these features are not specific, and hence most patients will need a surgical lung biopsy which shows characteristic extensive lymphyocytic infiltration into the alveolar spaces. Treatment is both supportive and targeted towards treating the underlying condition (e.g. immunosuppression in patients with rheumatoid). Patients who are asymptomatic may need monitoring only. There is a small risk of patients with LIP progressing to lymphoma, and this may warrant long-term radiological follow-up.

Birt Hogg Dubé Syndrome

Birt Hogg Dubé syndrome is a rare cystic lung condition with an autosomal dominant inheritance [16]. It is due to a mutation in the gene encoding folliculin. Patients predominantly present with skin fibrofolliculomas, and the cystic changes in the lungs may be an incidental finding. When they do present with lung disease, a spontaneous pneumothorax may be the first finding, but some patients do present with non-specific symptoms including shortness of breath and cough. CT of the chest reveals thin-walled cystic lesions, and the condition is associated with renal tumours, which warrants ultrasound or CT scans of the abdomen every 2–3 years. A definitive diagnosis can be made through genetic testing for mutations in the folliculin gene, and current testing can detect up to 90% of mutations. There is no specific treatment for the lung, and management tends to be supportive only.

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