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18.14

Miscellaneous conditions

CONTENTS

18.14.1 Diffuse alveolar haemorrhage

S.J. Bourke and G.P. Spickett

ESSENTIALS

Diffuse alveolar haemorrhage is characterized by acute respiratory failure, diffuse air space shadowing on the chest radiograph, haemoptysis, and anaemia. There are many different causes including immune-mediated diseases (notably pulmonary vasculitis, connective tissue diseases and Goodpasture's syndrome) and non-immune-mediated disease (cardiac failure, infection, coagulation disorders, thrombolytic therapy, toxins, and barotrauma). Prompt identification of the underlying cause is important in directing specific treatments.

Goodpasture's syndrome is an autoimmune disorder characterized by alveolar haemorrhage and glomerulonephritis due to antibasement membrane antibodies. Renal failure is usually the dominant feature, but alveolar haemorrhage can precede renal involvement.

Idiopathic pulmonary haemosiderosis is a rare disorder of unknown cause with recurrent alveolar bleeding, which may provoke pulmonary fibrosis, and anaemia.

Introduction

Diffuse alveolar haemorrhage typically presents as a combination of acute respiratory failure, bilateral infiltrates on a chest radiograph, haemoptysis, and anaemia. It is not a distinct disease entity but a clinical pattern with many different causes. Management is crucially dependent on recognizing that the lung infiltrates are due to alveolar haemorrhage rather than pulmonary oedema, infection, or inflammation.

Bronchoscopy with bronchoalveolar lavage is often important in demonstrating acute bleeding at the alveolar level, or haemosiderin-laden macrophages in chronic cases, and in excluding infection or a bronchial cause of haemorrhage. Some patents presenting in respiratory failure may need endotracheal intubation and ventilation before bronchoscopy can be performed. Considerable amounts of blood can accumulate in the alveoli before giving rise to haemoptysis, which is therefore not always apparent at presentation. Characteristically blood in the alveoli causes an elevation of the carbon monoxide transfer factor ($T_L$co) and transfer coefficient (*K*co) as red blood cells in the alveoli bind carbon monoxide, but often patients are not sufficiently stable to undertake lung function tests.

The causes of diffuse alveolar haemorrhage are diverse but can be broadly classified into immune-mediated and nonimmune-mediated causes (**Box 18.14.1.1**). The clinical context is crucial in identifying the aetiology and a careful assessment is needed to identify any provoking factors (drugs, tobacco smoke, inhaled toxins)

Box 18.14.1.1 Causes of diffuse alveolar haemorrhage

Immune-mediated diseases

Vasculitis

- Granulomatosis with polyangiitis (previously known as Wegener's disease)
- Eosinophilic granulomatosis with polyangiitis (previously known as Churg–Strauss syndrome)
- Microscopic polyangiitis
- Polyarteritis nodosa
- Takayasu's arteritis
- Pauci-immune pulmonary capillaritis

Connective tissue disease

- Systemic lupus erythematosus
- Rheumatoid disease
- Mixed connective tissue disease
- Systemic sclerosis
- Goodpasture's syndrome (antibasement membrane antibody disease)

Nonimmune-mediated diseases

Cardiac

- Left ventricular dysfunction
- Valvular heart disease
- Congenital cardiac anomalies
- Pulmonary veno-occlusive disease

Infection

- Staphylococcal pneumonia
- Leptospirosis

Coagulation disorders

- Thrombocytopaenia
- Thrombolytic therapy
- Disseminated intravascular coagulation

Toxic

- Cannabis, cocaine, tobacco
- Volatile hydrocarbon glue solvents
- Drugs (penicillamine, mitomycin C, amiodarone)

Idiopathic

- No cause identified
- Idiopathic pulmonary haemosiderosis

or any systemic diseases (cardiac, renal, connective tissue diseases). As can be seen in Box 18.14.1.1, diffuse alveolar haemorrhage (Fig. 18.14.1.1) may be a manifestation of many diseases, but is a defining characteristic of two, Goodpasture's syndrome and idiopathic pulmonary haemosiderosis.

Immune-mediated alveolar haemorrhage

Immune-mediated diseases account for about 35% of cases of diffuse alveolar haemorrhage and include primary pulmonary vasculitis, vasculitis secondary to connective tissue diseases, and antibasement membrane antibody disease (Goodpasture's syndrome). In some of these diseases both the lungs and kidneys are involved such that they present as a pulmonary-renal syndrome.

Fig. 18.14.1.1 Radiograph showing gross alveolar shadowing following severe pulmonary haemorrhage in a 60-year-old man with systemic vasculitis.

Pulmonary vasculitis

Granulomatosis with polyangiitis (Wegener's disease), eosinophilic granulomatosis with polyangiitis (Churg–Strauss syndrome), and microscopic polyangiitis are usually associated with antineutrophil anticytoplasmic antibodies (ANCA). Granulomatosis with polyangiitis commonly causes a necrotizing glomerulonephritis and is associated with necrotizing inflammation of the nasopharynx, the central airways, the lung parenchyma, and the pulmonary vessels. Biopsy of the kidneys or nasopharynx is usually more appropriate than lung biopsy, and the ANCA antibodies are usually of the cytoplasmic type (C-ANCA) and are directed against proteinase-3. By contrast, microscopic polyangiitis does not typically involve the upper respiratory tract and is not granulomatous, and the ANCA antibodies are perinuclear (P-ANCA), directed against the myeloperoxidase of neutrophil cytoplasmic granules. In eosinophilic granulomatosis with polyangiitis there is an allergic granulomatous angiitis associated with high IgE levels and hypereosinophilia in a patient with asthma.

Other vasculitic disorders rarely cause diffuse alveolar haemorrhage, but include polyarteritis nodosa, Henoch–Schönlein purpura, and Takayasu's arteritis. Pulmonary vasculitis with alveolar haemorrhage may also rarely be secondary to connective tissue diseases such as systemic lupus erythematosus, rheumatoid disease, mixed connective tissue disease, IgA nephropathy, systemic sclerosis, and primary antiphospholipid syndrome.

Goodpasture's syndrome

Goodpasture's syndrome is a rare autoimmune disorder characterized by diffuse alveolar haemorrhage and glomerulonephritis due to antibasement membrane antibodies. These antibodies are mainly directed against the α-3 chain of type IV collagen in the alveolar and glomerular basement membranes. Damage to this domain of collagen may elicit an autoimmune response. Increased susceptibility is

associated with HLA DRB11 501 and DRB11 502 alleles, while protection is associated with HLA DR1 and DR7.

Acute glomerulonephritis with renal failure is usually the dominant feature of antibasement membrane antibody disease, but this is sometimes associated with alveolar haemorrhage, which can rarely precede renal involvement. Alveolar haemorrhage is strongly associated with cigarette smoking, or sometimes with inhalation of other toxins such as cocaine or volatile hydrocarbon glue solvents. This suggests that inhaled toxins enhance pulmonary endothelial damage and thus allow the initiation of autoimmunity or the access of existing autoantibodies to the basement membrane.

The usual respiratory presentation is with cough, breathlessness, and haemoptysis, with diffuse shadowing on the chest radiograph. Renal function may be normal initially but can deteriorate rapidly. The diagnosis is established by the detection of antibasement membrane antibodies in the serum or as linear deposits along the basement membrane by immunofluorescence of glomeruli on renal biopsy, or rarely on lung biopsy in cases without renal involvement at presentation. Prognosis generally depends more on the renal effects than the pulmonary effects. See Chapter 21.8.7 for further discussion.

Nonimmune-mediated alveolar haemorrhage

Diffuse alveolar haemorrhage can occur due to many diverse nonimmune diseases which need to be sought and considered in the differential diagnosis. In a series of 112 consecutive patients with diffuse alveolar haemorrhage, nonimmune causes accounted for 65% of cases. These included cardiac disease in 29%, a diverse range of conditions in 23% (infection, toxins, drugs, coagulation disorders, barotrauma), and in 12% the cause was classified as idiopathic.

Chronic pulmonary venous congestion is a mechanism of alveolar haemorrhage in many cardiac diseases such as left ventricular dysfunction, valvular heart disease, pulmonary veno-occlusive disease, and in congenital cardiac anomalies. Alveolar haemorrhage may occur as part of severe infections, notably in patients with Staphylococcal pneumonia, but also in other infections such as leptospirosis, invasive aspergillosis, and HIV. Bleeding disorders such as thrombocytopaenia, coagulopathies, disseminated intravascular coagulation, and thrombolytic therapy can precipitate alveolar haemorrhage. Drugs (amiodarone, methotrexate, mitomycin C, penicillamine) or inhaled toxins (cannabis, cocaine, volatile hydrocarbon glue solvents, mycotoxins from moulds) have all been associated with alveolar haemorrhage. Barotrauma with haemorrhage can occur in scuba diving or as a complication of mechanical ventilation and general anaesthesia. A careful search for provoking factors and underlying diseases is important in deciding on the best management.

Idiopathic pulmonary haemosiderosis

This is a rare cause of alveolar haemorrhage of unknown aetiology which particularly affects children and young adults, with recurrent episodes of haemoptysis resulting in iron-deficiency anaemia.

Recurrent alveolar haemorrhage results in cough with haemoptysis and breathlessness, sometimes associated with fever and (in children) failure to thrive. During acute bleeds, the chest radiograph and CT scan show a nonspecific appearance of intra-alveolar blood. The alveolar blood may act as a fibrogenic stimulus resulting in diffuse pulmonary fibrosis, with a restrictive ventilatory defect and impaired gas transfer. Characteristically lung biopsy shows haemosiderin-laden macrophages with varying degrees of fibrosis, but does not show vasculitis or features of any other cause of alveolar haemorrhage. Antibasement membrane antibodies are not present, and the electron microscopic appearance of the basement membrane shows no consistent abnormality.

Some cases previously classified as idiopathic pulmonary haemosiderosis may have been a consequence of vasculitis at the pulmonary capillary level (pauci-immune pulmonary capillaritis). Some cases may result from inhalation of toxins from moulds such as the stachybotrys mould, which may contaminate wet or damp accommodation, and which releases a particularly potent toxin with haemorrhagic properties. Idiopathic pulmonary haemosiderosis is also associated with cow's milk allergy and coeliac disease.

The rarity of the disease means that treatment regimens and prognosis are poorly defined and based mainly on case reports. In children with associated cow's milk allergy or coeliac disease, avoidance of milk or gluten usually results in improvement. In adults the prognosis is more variable and protracted, with some patients responding to corticosteroids and other immunosuppressant drugs. In longstanding cases, interstitial lung fibrosis may develop. About a quarter of patients go on to develop some form of systemic autoimmune disease.

Management

Treatment of alveolar haemorrhage is initially mainly supportive, with stabilization of the patient's respiratory and haemodynamic status, and attention to any coagulation abnormalities or renal dysfunction. In a large case series of consecutive patients with alveolar haemorrhage, 77% required admission to an intensive care unit, 18% needed endotracheal intubation and ventilation, and 16% renal replacement therapy. In-hospital mortality was 24%. Prompt identification of the underlying cause allows the initiation of appropriate specific treatment.

For patients with vasculitis, induction of remission is usually achieved by a combination of corticosteroids (typically intravenous methylprednisolone 500–1000 mg daily for 3–5 days, followed by prednisolone 1 mg/kg/day orally) and cyclophosphamide (typically 2 mg/kg/day orally or 15 mg/kg intravenously in pulses at 3-weekly intervals). As clinical improvement occurs, the dose of immunosuppressants is gradually reduced. Alternative immunosuppressants such as rituximab, azathioprine, or methotrexate may be used in patients who are refractory to initial treatment or as steroid-sparing agents.

Goodpasture's syndrome with pulmonary haemorrhage is usually treated by a combination of plasmapheresis, corticosteroids, and cyclophosphamide. Plasmapheresis gives rapid removal of antibodies from the circulation and immunosuppressants reduce antibody synthesis. Some patients with idiopathic pulmonary haemosiderosis also appear to respond to immunosuppressants.

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18.14.2 Eosinophilic pneumonia

S.J. Bourke and G.P. Spickett

ESSENTIALS

Eosinophilic pneumonia is characterized by eosinophilic inflammation of the alveoli, usually with an accompanying eosinophilia of peripheral blood. The diagnosis should be considered when infiltrates on a chest radiograph are associated with blood eosinophilia, and is confirmed by demonstrating an excess of eosinophils in bronchoalveolar lavage fluid.

Aetiology—before concluding that the cause is 'idiopathic', the following must be considered: (1) parasitic infestation with blood-borne parasites such as (in tropical eosinophilia) filarial worms; (2) adverse drug reaction; (3) asthma; (4) allergic bronchopulmonary mycosis; (5) vasculitis, notably eosinophilic granulomatosis with polyangiitis (previously known as Churg–Strauss syndrome); (6) hypereosinophilic syndrome, a rare haematological disorder; and (7) other disorders known to be associated with eosinophilic pneumonia.

Management—causal factors need to be treated, but eosinophilic pneumonia otherwise often responds well to corticosteroid medication.

Table 18.14.2.1 The spectrum of eosinophilic pneumonia

Simple pulmonary eosinophilia
Chronic eosinophilic pneumonia
Acute eosinophilic pneumonia (Löffler's syndrome)
Drug-induced pulmonary eosinophilia
Tropical/parasite-induced eosinophilic pneumonia
Allergic bronchopulmonary aspergillosis
Eosinophilic granulomatosis with polyangiitis
Hypereosinophilic syndrome

Eosinophilic pneumonia encompasses a spectrum of conditions characterized by eosinophilic inflammation of the lung, often with blood eosinophilia. There are diverse provoking factors resulting in a confusing range of overlapping conditions.

Introduction

Eosinophilic pneumonia is characterized by eosinophilic inflammation of the lung, usually in association with peripheral blood eosinophilia (>0.45 × 10^9/litre) such that the presentation is often as pulmonary infiltrates on the chest radiograph with blood eosinophilia (PIE syndrome).

Several descriptive terms are used to classify the diverse range of clinical syndromes, but there are often overlapping features (Table 18.14.2.1). The initial focus is on identifying any provoking factors and excluding other diseases. Particular attention should be paid as to whether the patient been in areas where parasitic diseases are endemic, has pre-existing asthma or atopy, has recently started medications, has contact with pets, or has features of systemic disease or vasculitis. Important aspects of eosinophilic pneumonia to consider are:

- It may arise acutely and resolve quickly over a matter of days—acute eosinophilic pneumonia, Löffler's syndrome, simple pulmonary eosinophilia.
- It may arise gradually and persist for many months, leading sometimes to pulmonary fibrosis or fixed airway obstruction—chronic eosinophilic pneumonia.
- It may be a consequence of allergy, particularly to blood-borne parasites (tropical eosinophilia), inhaled moulds (allergic bronchopulmonary mycosis), or other common environmental allergens.
- It is often due to drugs, including prescribed medications, over-the-counter medications, and illicit substances.
- It is often associated with asthma—asthmatic eosinophilia.
- It may be associated with pulmonary vasculitis— eosinophilic granulomatosis with polyangiitis.
- It may be a component of the hypereosinophilic syndrome.
- It may seem to be idiopathic.

Since there is often overlap, there is limited benefit from using any classification system; the important issue is to identify potentially remediable causes, and to exclude infection or other causes before starting treatment with corticosteroids.

Diagnosis

In practice the finding of blood eosinophilia in association with pulmonary infiltrates on a chest radiograph provides a valuable

clue that pneumonia of infectious origin may not be the diagnosis. Once suspected, eosinophilic pneumonia is most conveniently confirmed by demonstrating an excess of eosinophils in bronchoalveolar lavage fluid in the absence of pathogenic microorganisms. Sometimes sputum alone is sufficient, whether expectorated spontaneously or induced. Alternatively, an excess of alveolar eosinophils is revealed in lung biopsy tissue. Not surprisingly, the use of CT scanning in subjects with confirmed eosinophilic pneumonia has shown that episodes of recurrent pulmonary infiltration occur more frequently than can be detected from plain chest radiographs. As different segments of lung become involved the infiltrates may characteristically 'migrate' from one to another.

Once eosinophilic pneumonia is confirmed, a variety of possible causes should be considered before it is assumed to be idiopathic in origin and before empirical treatment with corticosteroids is administered. Look for evidence of:

- parasitic infestation
- administration of drugs
- inhaled tobacco smoke, cocaine, marijuana
- asthma
- allergic bronchopulmonary mycosis (particularly aspergillosis)
- other manifestations of vasculitis
- other manifestations of the hypereosinophilic syndrome
- other disorders known to be associated with eosinophilic pneumonia

Treatment

Eosinophilic pneumonia is a very distinct type of interstitial lung disease in that the lung architecture is usually preserved such that there is often a complete response to treatment with corticosteroids without any permanent lung damage. Treatment may need to be prolonged (6 months or more) in the chronic forms of the disorder. The importance of identifying whether it is associated with the aforementioned causal factors listed lies with the additional need to treat these also, otherwise eosinophilic pneumonia may not respond adequately to steroid therapy and the associated diseases may produce other manifestations.

Particular forms of eosinophilic pneumonia

Acute eosinophilic pneumonia (Löffler's syndrome, simple pulmonary eosinophilia)

The essential features are transitory migratory pulmonary shadows associated with modest peripheral eosinophilia in patients with a mild self-limiting illness. Some cases are asymptomatic and discovered incidentally. Most patients present with cough, sometimes with oddly yellowish sputum containing an abundance of eosinophils, and a few have general malaise and a mild fever. The pulmonary shadows reflect fan-shaped areas of consolidation, often peripheral and sometimes rather nodular, which last a few days only and appear haphazardly in various lobes, seldom following a truly segmental pattern. In some cases they are single and in others they are multiple. The peripheral eosinophilia is obvious but rarely gross; a differential of more than 20% in a modestly raised total white cell count is unusual and more often the absolute eosinophil count ranges between 1×10^9 and 2×10^9/litre (normal $<0.45 \times 10^9$/litre). Patients are often atopic and may have other manifestations of an atopic diathesis, such as asthma, urticaria, and angio-oedema.

Allergic reactions to parasites or drugs are the best recognized forms, but sometimes no provoking factor is identified. Eosinophilic pneumonia may be an allergic reaction to blood-borne parasites migrating through the lung, particularly larvae of *Ascaris lumbricoides* and (occasionally) *A. suum*. Ancylostoma, strongyloides, taenia, trichinella, and trichuris may also cause eosinophilic pneumonia. Drugs form the second major aetiological group. Löffler's syndrome is described after administration of aspirin, amiodarone, angiotensin converting enzyme inhibitors, β-blockers, methotrexate, nitrofurantoin, imipramine, penicillin, *p*-aminosalicylic acid, sulphonamides, toxic smoke, and lymphangiography contrast medium.

Successful management requires the eradication of any parasites or the cessation of relevant medication, as well as the administration (if necessary) of oral corticosteroids.

Tropical eosinophilia

Eosinophilic pneumonia in tropical climates is often a consequence of migrating larvae of the filarial worms *Wuchereria bancrofti* and *Brugia malayi*. The effects are fundamentally similar to those of Löffler's syndrome, but tend to be more persistent and more serious, are more often associated with asthma, and may be associated with systemic symptoms of weight loss, persistent fever, and lymphadenopathy. The peripheral eosinophil count tends to be greater than in Löffler's syndrome ($>3 \times 10^9$/litre), and the total serum IgE level is markedly elevated. With chronicity, pulmonary fibrosis may develop. A cure is to be expected with antifilariasis medication (e.g. diethylcarbamazine).

Chronic eosinophilic pneumonia (prolonged pulmonary eosinophilia)

Eosinophilic pneumonia persisting for more than a month is distinguished from the more transitory Löffler's syndrome, although its clinical characteristics are fundamentally similar. As with eosinophilic pneumonia associated with tropical filariasis, it tends to be more persistent and more serious than Löffler's syndrome, and may be associated with systemic symptoms, such as fever, malaise, and fatigue. It can sometimes progress to pulmonary fibrosis. It may last for several months and be associated additionally with eosinophilic pleural effusion, focal skin lesions, atopic manifestations such as rhinitis, sinusitis, and angio-oedema, hepatosplenomegaly, and even hepatic necrosis. The pulmonary disease is often extensive, and may cause hypoxaemia as well as dyspnoea. A curious peripheral radiographic distribution of infiltrates, dubbed a 'negative photographic image of pulmonary oedema', is particularly suggestive of chronic eosinophilic pneumonia but occurs in only a few cases. The radiological abnormalities tend to recur and last for weeks or months, and like the shadows of Löffler's syndrome may vary in site during the course of the illness.

Chronic eosinophilic pneumonia is more commonly idiopathic than Löffler's syndrome, but may also be a consequence of parasite infestation (e.g. tropical filariasis) or drug hypersensitivity. Case reports have identified aminoglutethimide, BCG vaccination, bicalutamide, captopril, chlorpropamide, clarithromycin, clomipramine, dapsone, ethambutol, ibuprofen, meloxicam, mesalazine, minocycline, nitrofurantoin, perindopril, progesterone, sertraline, sotalol, sulphonamides, trimethoprim, and venlafaxine as

possible causes. Peripheral blood eosinophilia is less consistent with chronic compared with acute forms of eosinophilic pneumonia, although is often of greater level (>1 × 10^9/litre).

When a definitive cause is identified, appropriate specific management should follow, but often no cause is evident and oral corticosteroid therapy should be given. Responses are often dramatic, but recurrences are common if treatment is discontinued within 6 to 12 months. There may be a persistent mixed obstructive and restrictive loss of ventilatory function, and radiographic evidence of persistent pulmonary fibrosis.

Eosinophilic pneumonia with asthma

Eosinophilic pneumonia is commonly associated with asthma, even in the absence of parasite infestation or drug hypersensitivity. In a study of 53 cases, asthma preceded eosinophilic pneumonia in about half, and then worsened; in the remainder it arose by similar proportion either contemporaneously or within about 2 years. Two particular associations with asthma are noteworthy.

Allergic bronchopulmonary mycosis

When fungal hypersensitivity develops in atopic subjects with asthma, additional manifestations may occur in the lung: these include eosinophilic pneumonia, mucoid impaction, bronchiectasis, and pulmonary fibrosis. The ensuing syndrome of allergic bronchopulmonary mycosis occurs most commonly with *Aspergillus fumigatus*, though has been reported with other aspergillus, candida, curvularia, and helminthosporium species. It accounts for most cases of eosinophilic pneumonia with asthma in the United Kingdom and is best considered a complication of atopic asthma, appearing to result from airway colonization by the relevant mould. The mechanism, however, is clearly one of hypersensitivity, not infection or invasion, and both IgE and IgG antibodies are necessary to support its diagnosis. Allergic bronchopulmonary aspergillosis is also common in patients with cystic fibrosis lung disease.

In acute phases there is patchy obstruction of bronchi with inspissated mucus that, if expectorated, appears as brown rubbery lumps in the sputum (plugs). Fungal hyphae may be recovered from them, indicating that fungal growth has occurred within the airway. This impaction of mucus in one or more bronchi leads to atelectasis of segments or lobes of the lung, and is often associated with eosinophilic pneumonia. The radiographic appearances are of fleeting pulmonary infiltrates (Fig. 18.14.2.1).

The condition usually responds well to corticosteroids, a useful diagnostic feature being the expectoration of plugs during this period of resolution. In the medium term the involved bronchi (generally proximal) may become bronchiectatic, leading in turn to the characteristic features of bronchiectasis (productive cough, intermittent haemoptysis). In the longer term, pulmonary fibrosis may ensue, particularly in the upper lobes and apices, so that the radiographic appearances resemble tuberculosis. If mucoid impaction and/or eosinophilic pneumonia become superimposed, the radiographic appearances may simulate active tuberculosis very closely. Suspicion of tuberculosis in an individual with atopic asthma should always prompt consideration of allergic bronchopulmonary mycosis.

Antifungal agents (itraconazole, voriconazole) decrease the antigen burden and the associated immune response, but need to be used in conjunction with corticosteroids. They are particularly useful in allowing a reduction in the dose of corticosteroids.

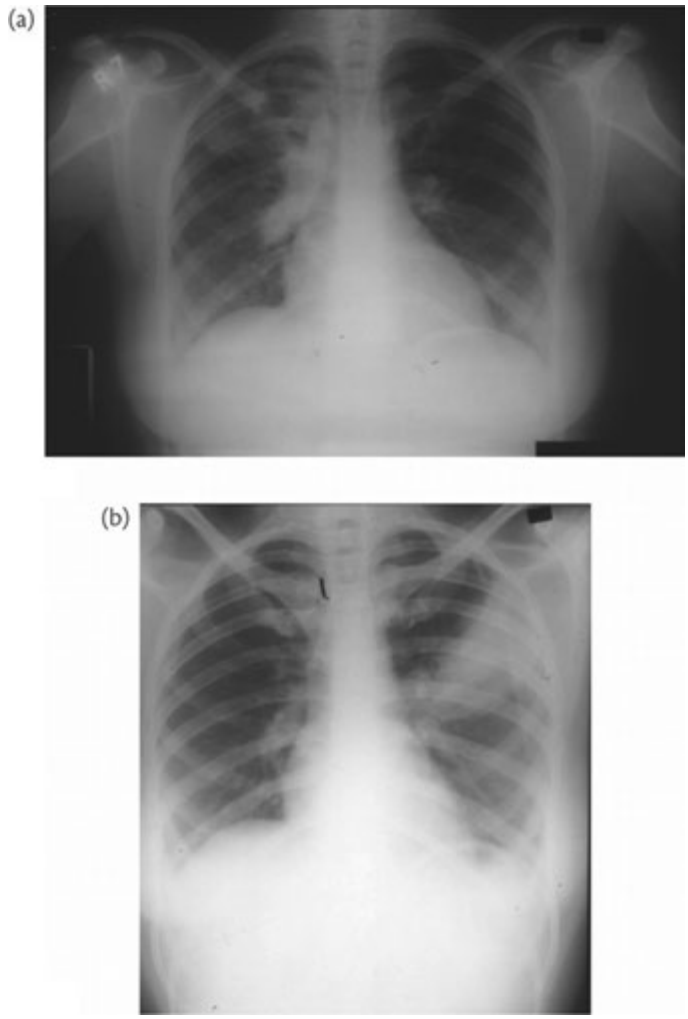

Fig. 18.14.2.1 Allergic bronchopulmonary aspergillosis: two radiographs taken 6 months apart from a woman with asthma, peripheral eosinophilia, and high titres of IgE and precipitating IgG antibodies to *Aspergillus fumigatus*.

Eosinophilic granulomatosis with polyangiitis

A much rarer association of eosinophilic pneumonia with asthma is that involving eosinophilic granulomatosis with polyangiitis. This is a vasculitic and granulomatous disorder that commonly involves lungs, gut, peripheral nerves, skin, and kidneys, and occasionally heart. It is characterized typically by asthma, eosinophilic pneumonia, and very high numbers of circulating eosinophils (>5 × 10^9/litre), but the pulmonary manifestations may additionally include haemorrhage and haemoptysis. Serological investigation may also demonstrate raised serum levels of IgE and eosinophil cationic protein, P-ANCA (perinuclear antineutrophil cytoplasmic antibodies) with myeloperoxidase activity (in most cases), and C-ANCA with proteinase-3 specificity (in a few cases). Autoantibodies against eosinophil granule enzymes have also been described. Pathologically there is vasculitis of small arteries and veins with necrotizing extravascular granulomas. Biopsy of affected tissue may be needed to confirm the diagnosis, and may be diagnostic even in the prevasculitic phase if there is characteristic eosinophilic infiltration of involved tissue. See Chapter 19.11.7 for further discussion.

Hypereosinophilic syndrome

Hypereosinophilic syndrome is a rare haematological disorder with sustained overproduction of eosinophils in the bone marrow. It is characterized by blood eosinophilia exceeding 1.5×10^9/litre for at least 6 months, no identifiable cause after extensive investigation, and end organ damage associated with eosinophil infiltration. The heart, skin, and nervous system are the most common targets: the lungs are not commonly involved and hence hypereosinophilic syndrome is a particularly rare cause of eosinophilic pneumonia.

Hypereosinophilic syndrome is heterogenous, sometimes due to a myeloproliferative disorder or a clonal expansion of specific T cells, but often no cause is apparent. A bone marrow biopsy is usually an important investigation. In some cases an underlying mechanism has been identified, involving either tyrosine kinase activity or interleukin 5. An interstitial deletion on chromosome 4 can produce a 'fusion' gene by the fusion of the *PDGFRA* and *FIP1L1* genes, the new gene encoding a protein with tyrosine kinase activity that affects early myeloid differentiation. These findings are closely associated with eosinophilic leukaemia, and treatment with imatinib, interferon-α or hydroxycarbamide is effective in treatment. In lymphocytic hypereosinophilic syndrome, there is an abnormal clone of T cells which releases 'eosinophilic' cytokines, principally interleukin 5 (IL-5), that stimulate bone marrow generation and inhibit peripheral destruction. This condition is less likely to cause end organ dysfunction and is often readily controlled with corticosteroids. An anti-IL-5 monoclonal antibody (mepolizumab) may be effective in treating this form of hypereosinophilic syndrome.

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18.14.3 Lymphocytic infiltrations of the lung

S.J. Bourke

ESSENTIALS

Lymphocytic infiltrations of the lung arise from the proliferation of bronchus-associated lymphoid tissue, resulting in a spectrum of rare conditions ranging from benign polyclonal lymphoid interstitial pneumonia to monoclonal primary malignant lymphomas of the lung.

Lymphoid interstitial pneumonia is most commonly seen in Sjögren's syndrome or other connective tissue diseases, and in association with HIV infection, and is characterized by reticulonodular shadowing on CT imaging and (usually) a good response to corticosteroids.

Primary pulmonary lymphomas fall into three categories: lymphomatoid granulomatosis, low-grade B-cell lymphoma, and high-grade B-cell lymphoma. The latter require treatment with cytotoxic drugs and have a poor prognosis.

Introduction

Lymphoid tissue is usually inconspicuous or absent in normal lung tissue. Bronchus-associated lymphoid tissue develops as a reaction to exogenous stimuli such as smoking, infection, and antigen inhalation, or endogenous circulating antigens in autoimmune and connective tissue diseases. Reactive hyperplasia of this bronchus-associated lymphoid tissue occurs in conditions such as chronic infections, immune deficiency syndromes, obstructive pneumonias, and collagen vascular diseases. Both benign lymphoid infiltrations of the lung, such as lymphoid interstitial pneumonia (LIP), and neoplastic infiltrations in primary pulmonary lymphomas, are related to lymphoid hyperplasia of bronchus-associated lymphoid tissue (**Box 18.14.3.1**).

Lymphoid interstitial pneumonia

Lymphoid (lymphocytic) interstitial pneumonia (LIP) is a rare disease in which pulmonary lymphoid hyperplasia progresses to a diffuse polyclonal lymphoid cell infiltration, surrounding the airways as follicular bronchiolitis, and expanding the interstitium of the lung. In some cases it is idiopathic with no identifiable cause, but it is most commonly associated with collagen vascular diseases such as Sjögren's syndrome, systemic lupus erythematosus,

Box 18.14.3.1 Lymphocytic infiltrations of the lung

Reactive polyclonal lymphoid infiltration

- Lymphoid interstitial pneumonia
- Follicular bronchiolitis
- Lymphoid hyperplasia

Pulmonary lymphomas

Secondary lymphoma involving the lung

- Non-Hodgkin's lymphoma
- Hodgkin's lymphoma

Primary pulmonary lymphomas

- Lymphomatoid granulomatosis (angiocentric lymphoma)
- Bronchus-associated lymphoma (high/low grade)
- HIV-related lymphoma
- Post-transplantation lymphoproliferative disorder

rheumatoid disease, autoimmune diseases such as primary biliary cirrhosis, myasthenia gravis and Hashimoto's thyroiditis, and immune deficiency states such as common variable immunodeficiency and HIV infection. It has also been described in relation to drugs such as phenytoin and captopril. Epstein–Barr virus has been isolated in some cases.

It most commonly presents in middle age and is more common in women. Symptoms usually include breathlessness, dry cough, and sometimes systemic symptoms of weight loss and malaise. Crackles may be audible. Features of an underlying autoimmune or systemic disease may be present, and should be sought. In HIV infection LIP is most common in children and is rare in adults. It may occur relatively early in the course of HIV infection, when the CD4+ T lymphocytes count is still within the normal range.

The chest radiograph shows nonspecific reticulonodular opacities, usually most apparent at the lung bases. CT imaging shows ground-glass attenuation with centrilobular nodules and thickened bronchovascular bundles and interlobular septa, sometimes with cysts. Lung function tests typically show restriction of lung volumes and impaired gas diffusion. Bronchoalveolar lavage shows lymphocytosis. Surgical biopsy is often required to confirm the diagnosis. The histology shows that the alveolar septa are extensively infiltrated by lymphocytes, plasma cells, and histiocytes with associated type II cell hyperplasia. The differential diagnosis includes nonspecific interstitial pneumonia, hypersensitivity pneumonitis, usual interstitial pneumonia, and pulmonary lymphoma. Careful immunohistochemistry and molecular analysis are required to differentiate LIP from lymphoma. When a histological diagnosis of LIP has been established, investigations for associated diseases should be undertaken including HIV testing and auto-antibodies tests for connective tissue diseases. There is often polyclonal elevation of IgG and IgM but sometimes hypogammaglobulinaemia and monoclonal gammopathies.

The clinical course of LIP is very variable and reflects also the course of the underlying disease. In many cases the disease is indolent, with little progression over many years, but about one-third of cases progress to pulmonary fibrosis. LIP is usually treated by corticosteroids, often with a good response. In HIV-associated LIP, antiretroviral treatment results in improvement. Lung transplant has been performed in very rare cases which have failed to respond to corticosteroids and progressed to end-stage fibrosis.

Lymphoma

The lung parenchyma may be involved in disseminated nodal lymphomas of all types but the clinical presentation of these secondary lymphomas is usually dominated by disease at other sites (Chapter 22.4.3). Primary pulmonary lymphoma arises from bronchus-associated lymphoid tissue rather than lymph nodes, and is very rare, accounting for less than 0.5% of all primary lung neoplasms. Classification of primary pulmonary lymphomas is complex and different from nodal lymphomas, but generally falls into the categories of lymphomatoid granulomatosis (angiocentric lymphoma), low-grade B-cell lymphoma, and high-grade B-cell lymphoma. It seems that prolonged stimulation of bronchus-associated lymphoid tissue with a high turnover of B-cells in conditions such as Sjögren's syndrome, autoimmune disease, and Epstein–Barr virus infection, may contribute to the development of lymphoma. Immunosuppression may also be an important factor, particularly in patients who have undergone organ transplantation, or in those with HIV infection. Additional neoplastic change seems to occur in prolonged lymphoid hyperplasia, with chromosomal translocations leading to constitutive activation of signalling pathways progressing to lymphoproliferative change and lymphomatous transformation. Post-transplant lymphoproliferative disease may result from a decreased T-cell immune response to the Epstein–Barr virus induced by immunosuppression, and includes a spectrum of disease from lymphoid hyperplasia to high-grade lymphoma. The Epstein–Barr virus latent membrane protein has been shown to have oncogenic properties and may be a key factor in the development of some pulmonary lymphomas.

Lymphomatoid granulomatosis (angiocentric lymphoma)

Lymphomatoid granulomatosis is considered separately as a unique type of lymphoproliferative disorder with a propensity for blood vessel destruction, which particularly affects the lungs. It is now classified as an angiocentric, Epstein–Barr virus-associated B-cell lymphoma rather than a vasculitis. The lungs are the most commonly involved site, but it is a multisystem disease which can also involve the skin, kidney, liver, and central and peripheral nervous systems. Although it is a lymphoproliferative disorder it is rare for it to involve the lymph nodes, spleen, or bone marrow.

The disease is very uncommon in childhood but occurs throughout adult life, particularly in middle age, with a slight predilection for males. Patients often present with prominent systemic symptoms of fever, weight loss and general malaise, in addition to chest symptoms such as cough, haemoptysis, and chest pain. About a quarter have neurological symptoms and half develop skin lesions. Lymphadenopathy is not usually present.

The chest radiograph and CT imaging typically show multiple rounded masses, sometimes with cavitation, such that the disease mimics metastatic carcinoma, infection, or vasculitis (Fig. 18.14.3.1). Surgical biopsy of a lung lesion is usually necessary to establish the diagnosis. Histologically the disease is characterized by atypical B-cells infiltrating around the bronchovascular and perivascular

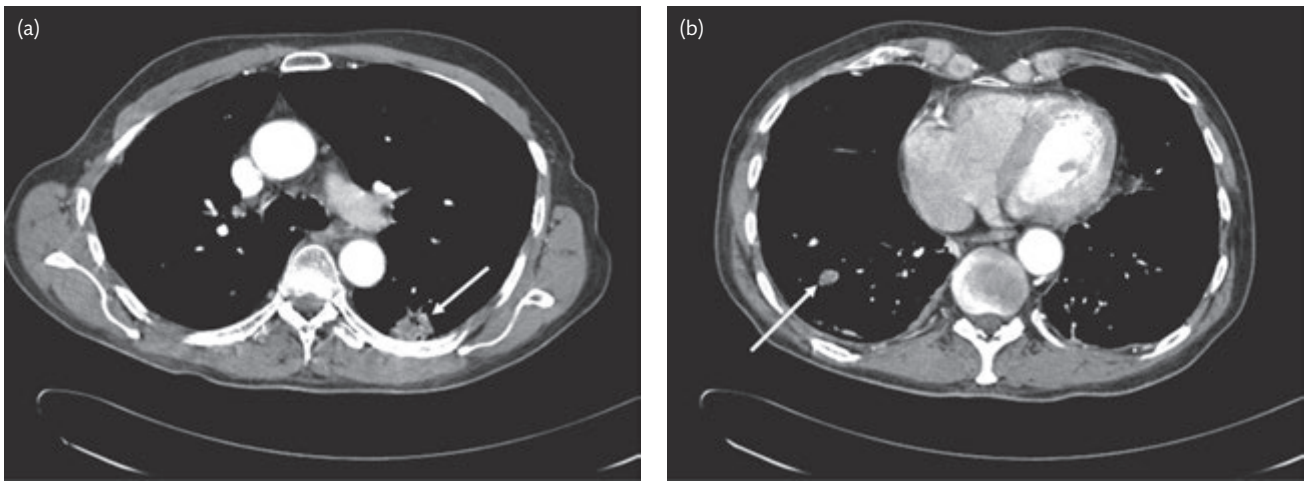

Fig. 18.14.3.1 CT of a patient with lymphomatoid granulomatosis showing (a) a cavitating mass in the left lower lobe (arrow) and (b) a further mass in the right lower lobe (arrow).

regions, with associated T-cells, plasma cells, and histiocytes. Immunocytochemistry and molecular analysis show that the B-cells are clonal and malignant, and evidence of Epstein–Barr virus infection may be present. Vascular infiltration is a prominent feature and patients may have haemoptysis and lung haemorrhage.

Patients have sometimes been given corticosteroids because of a suspicion of a vasculitic or inflammatory disease, and temporary improvement in symptoms sometimes occurs from treatment with corticosteroids alone, but this is an aggressive malignant lymphoma with a high mortality and requires cytotoxic therapy. Chemotherapy usually involves drugs such as cyclophosphamide, doxorubicin, vincristine, prednisolone, and rituximab, but regimens are not well established because of the rarity of the disease. The prognosis is generally poor with a 5-year mortality of 50–70%.

Low-grade B-cell lymphoma

Low-grade B-cell non-Hodgkin's lymphomas account for about 80–90% of primary lymphomas affecting the lung parenchyma. They generally arise in middle aged or elderly adults from mucosa-associated lymphoid tissue of the bronchi, and may occur after a prolonged period of antigenic stimulation and high B-cell turnover associated with Sjögren's syndrome, dysgammaglobulinaemia, amyloid deposition, collagen vascular disease, and HIV infection.

Presentation is commonly as an incidental finding on a chest radiograph, before symptoms have developed. When symptoms do occur, they include cough, haemoptysis, chest pain and (occasionally) breathlessness, and there may be systemic symptoms such as fever, malaise, and weight loss. The chest radiograph and CT imaging usually shows multiple parenchymal nodules with diameters ranging up to a few centimetres. Sometimes spread outside the bronchi and pulmonary vessels, but within the bronchovascular bundles, may leave the airway patent and so produce air bronchograms within the tumorous opacities. In a few cases there is a diffuse nodular infiltration.

The clinical presentation and radiological features often cause confusion, hence biopsy is required to establish a diagnosis and to demonstrate a B-cell clone and the grade of activity of the lymphoma. These low-grade lymphomas can behave indolently and initial observation may be appropriate, before considering cytotoxic chemotherapy. The prognosis is generally good with an estimated 5- and 10-year survival rate of 90% and 72%, respectively.

High-grade B-cell lymphoma

High-grade B-cell non-Hodgkin's lymphomas account for 10–20% of primary lymphomas affecting the lung parenchyma. They particularly occur in immunosuppressed patients in the context of HIV infection or after organ transplantation.

The more aggressive nature of high-grade disease is reflected by the greater likelihood of respiratory and systemic symptoms. Multifocal involvement may cause cough, dyspnoea, haemoptysis, and chest pain, often with systemic symptoms of weight loss, fever, and malaise. Local infiltration by lymphomatous masses may produce atelectasis of a segment or lobe of lung, sometimes with pleural effusions.

The prognosis of high-grade pulmonary lymphoma is much less favourable than that of low-grade disease. In post-transplant lymphoma associated with Epstein–Barr virus, a reduction in immunosuppression and antiviral treatment, such as ganciclovir or valganciclovir, may be appropriate. Chemotherapeutic regimens for the treatment of pulmonary lymphoma are similar to those used in other lymphomas, including drugs such as rituximab, chlorambucil, cyclophosphamide, fludarabine, doxorubicin, and vincristine, administered under specialist oncology supervision.

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18.14.4 Hypersensitivity pneumonitis

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ESSENTIALS

Hypersensitivity pneumonitis is an immune-mediated lung disease in which the repeated inhalation of certain antigens provokes a hypersensitivity response, with granulomatous inflammation in the distal bronchioles and alveoli of susceptible people. A diverse range of antigens including bacteria (*Thermophilic actinomycetes*), fungi (*Trichosporon cutaneum*), animal proteins (bird antigens), mycobacteria, and chemicals may cause the disease. The commonest forms are bird fancier's lung, farmer's lung, humidifier lung, and metal-working fluid pneumonitis. In some cases no antigen is identified.

Acute disease is characterized by recurrent episodes of breathlessness, cough, fevers, malaise, and flu-like symptoms occurring 4–8 hours after antigen exposure. Fever and basal crackles are the main physical signs. This form of hypersensitivity pneumonitis is most commonly seen where there is intermittent high-level antigen exposure, as in the case of pigeon fancier's lung or farmer's lung. Most patients recover fully from each acute exacerbation within a day or so, and if the cause is recognized and further exposure avoided there is little risk of persisting pulmonary dysfunction.

Chronic disease is characterized by the insidious development of dyspnoea and persistent pneumonitis, sometimes progressing to lung fibrosis. This form of the disease is typically seen following long-standing low-level antigenic exposure, such as occurs in a person who keeps a single budgie (parakeet) in the home. Clinical features are similar to those of other varieties of pulmonary fibrosis, but clubbing is uncommon. Permanent fibrotic lung damage can eventually lead to hypoxaemia, pulmonary hypertension, right heart failure, and death.

Investigation—the chest radiograph may be normal or show a ground-glass appearance; in subacute disease small reticular opacities may be seen; in chronic disease there is fibrosis. CT characteristically shows centrilobular nodules, mosaic air trapping, and ground-glass shadowing. Lung function studies typically show a restrictive pattern with impaired gas diffusion. IgG antibody against the provoking antigen indicates sufficient exposure for the disease to develop, but such antibodies are frequently found in subjects who are similarly exposed but clinically unaffected. Bronchoalveolar lavage typically shows a lymphocytic alveolitis, and lung biopsy shows peri-bronchocentric lymphocytic inflammation with poorly formed granulomas and sometimes fibrosis.

Management—complete cessation of contact with the provoking antigen is the safest advice for patients with hypersensitivity pneumonitis. This usually leads to resolution of the acute form of the disease. Corticosteroids hasten the rate of recovery, but do not alter the long-term outcome. Some patients with chronic hypersensitivity pneumonitis progress to severe fibrotic lung disease resembling idiopathic pulmonary fibrosis. If these patients fail to respond to corticosteroids and other immunosuppressive agents, lung transplantation is sometimes appropriate.

Introduction

Hypersensitivity pneumonitis (HP), previously known as extrinsic allergic alveolitis, is an immune-mediated lung disease in which the repeated inhalation of certain antigens provokes a hypersensitivity reaction with granulomatous inflammation in the distal bronchioles and alveoli of susceptible people. The essence of the disease is an interaction between specific inhaled antigens and the patient's immune system. It is therefore an allergic lung disease and it should be distinguished from several nonallergic inflammatory reactions such as inhalation fevers, toxic alveolitis, and organic dust toxic syndrome, which occur after a single exposure to an unusually high level of organic dust by toxic rather than immune mechanisms. By contrast, individual susceptibility is a characteristic feature of immune-mediate disease such as HP, and only a small percentage of those repeatedly exposed to the antigen develop the disease.

Aetiology

HP can be caused by a diverse range of antigens including bacteria (Thermophilic actinomycetes), fungi (*Trichosporon cutaneum, Aspergillus fumigatus*), animal proteins (bird antigens), mycobacteria (*Mycobacterium immunogenum*), and chemicals (di-isocyanates). Geographical, social, and occupational factors determine the particular types of HP found in different parts of the world (**Table 18.14.4.1**). Because of the great diversity and distribution of these antigens, many individuals are exposed to potential causes of HP as part of their occupational, home, or recreational environments.

Farmer's lung is regarded as the prototype of HP since the classic description by Campbell *et al.* in 1932. Occupations in which there is contact with mouldy vegetation are particularly associated with the disease, and specific syndromes have therefore been described, for example, in respect of farmers, mushroom workers, and sugar cane workers (bagassosis). Those exposed to raw wood products have been

Table 18.14.4.1 Agents reported to cause hypersensitivity pneumonitis

Agent	Source	Appellation (if any)
Microorganisms		
Acinetobacter woffii	Metal-working fluid	Machine worker's lung
Alternaria	Paper-mill wood pulp	Wood pulp worker's lung
Aspergillus sp.	Farm produce, maize (corn)	Farmer's lung
Aspergillus clavatus	Whisky maltings	Malt worker's lung
Aspergillus fumigatus	Vegetable compost, cork	Farmer's lung, suberosis
Aspergillus versicolor	Dog bedding (straw)	Dog house disease
Aureobasidium pullulans	Redwood/domestic cellar	Sequoiosis
Bacillus subtilis	Wood/cleaning preparations	
Candida albicans	Heated swimming pool; saxophonist lung	Saxophonist lung
Cephalosporium	Sewage	Sewage worker's lung
Cryptococcus albidus	Asian homes in humid summers	Summer-type hypersensitivity pneumonitis
Cryptostroma corticale	Maple	Maple bark stripper's lung
Debaryomyces hansenii	Home ultrasonic nebulizer	
Eurotium sp.	Metal-working fluid	Machine worker's lung
Fusarium sp.	Metal-working fluid/home	Machine worker's lung
Graphium	Redwood	Sequoiosis
Grifola fondosa	Maitake mushrooms	Mushroom worker's lung
Humicola fuscoatra	Domestic home	
Hypsizigus marmoreus	Mushrooms	Mushroom worker's lung
Lentinus edodes	Mushrooms	Mushroom worker's lung
Lycoperdon	Puffballs	Lycoperdonosis
Lyophyllum aggregatum	Mushrooms	Mushroom worker's lung
Merulius lacrymans	Domestic wood	
Mucor stolonifer	Paprika	Paprika splitter's lung
Mycobacterium sp.	Metal-working fluid	Machine worker's lung
Paecilomyces sp. (*nivea/variotii*)	Hardwood, oil heater	
Penicillium camemberti	Salami production	
P. *casei*	Cheese	Cheese washer's lung
P. *chrysogenum/cyclopium*	Domestic wood	
P. *citrinum*	Enoki mushroom cultivation	
P. *frequentens*	Cork	Suberosis
P. *nalgiovense*	Pork sausage mould	
P. *verrucosum*	Gorgonzola cheese	
Peziza domiciliana	Flooded basement	El Niño lung
Pleurotus ostreatus/eryngii	Mushrooms	Mushroom worker's lung
Pseudomonas fluorescens	Metal-working fluid	Machine worker's lung
Rhodotorula sp.	Ultrasonic humidifier	
Saccharomonspora viridis	Logging plant	
Sphingbacterium spiritvorum	Domestic steam iron	
Sporobolomyces	Horse barn straw	
Streptomyces albus	Soil/peat	
Thermophilic actinomycetes (*Saccharopolyspora rectivirgula, Thermoactinomyces vulgaris*)	Hay/straw/grain/mushroom compost/bagasse/heated water/domestic cellar/esparto grass	Farmer's lung Mushroom worker's lung Bagassosis Esparto plasterer's lung
Trichosporon cutaneum/ovoides	Asian homes in humid summers	Summer-type hypersensitivity pneumonitis

(continued)

Table 18.14.4.1 Continued

Agent	Source	Appellation (if any)
Miscellaneous bacteria/mycobacteria/fungi/amoebae/nematode debris	Air conditioners/humidifiers/tap water/showers/heated pools, saunas, tubs/metal fluids	Humidifier lung Ventilation pneumonitis Sauna taker's lung
Unknown	Roof thatch	New Guinea lung
Animals		
Arthropods (*Sitophilus granarius*)	Grain dust	Wheat weevil disease
Birds	Feather bloom/droppings	Bird fancier's lung
Fish	Fish meal	Fish meal worker's lung
Mammal pituitary (cattle, pig)	Pituitary extracts	Pituitary snuff taker's lung
Mammal hair	Fur	Furrier's lung
Mollusc shell	Nacre-button manufacture	
Urine (rodents)	Urinary protein	Rodent handler's lung
Vegetation		
Cabreuva	Wood dust	
Coffee	Coffee bean dust	Coffee worker's lung
Esparto grass	Plaster	Esparto plasterer's lung
Amorphophalus konjac	Konjac flour	Konnyaku maker's lung
Peat moss	Peat moss packaging plant	
Shimeji	Shimeji cultivators	
Tiger nut	Tiger nut dust	
Wood (*Gonystylus bacanus*)	Wood dust	Wood worker's lung
Chemicals		
Bordeaux mixture (fungicide)	Vineyards	Vineyard sprayer's lung
Cobalt dissolved in solvents	Tungsten carbide grinding	
Diphenyl methane diisocyanate	Plastics industry	
Hexamethylene diisocyanate	Plastics industry	
Methyl methacrylate	Dentistry	
Pauli's reagent	Laboratory	
Phthalic (or trimellitic) anhydride	Epoxy polyester powder paint	
Pyrethrum	Insecticide spray	
Tetrachloroethylene	Dry cleaning	
Toluene diisocyanate	Plastics industry	
Triglycidyl isocyanate	Plastics industry	
Trimellitic anhydride	Plastics industry	
Vanadium catalyst	Maleic anhydride manufacture	
Miscellaneous		
Hijikia fusiforme (algae)	Konjac flour	Konnyaku maker's lung
Pet fish food		

affected as maple bark stripper's lung, sequoiosis, and suberosis (cork worker's lung). Office and factory workers may be exposed to aetiological agents via humidifier or ventilation systems that have become contaminated with a variety of agents including bacteria, mycobacteria, fungi, protozoa (amoebae), and metazoa (nematode debris). Workers exposed to some reactive chemicals, such as di-isocyanates, may also develop HP, and here the chemical acts as a hapten combining with body proteins to produce larger antigenic molecules.

As practices change, some classic causes of HP have faded, but new syndromes are constantly being identified. Metal-working fluid pneumonitis has recently come to prominence because of outbreaks of HP in workers in car manufacturing, due to contamination of coolant and lubricant fluid.

The home environment may also be a rich source of the antigens of HP. Budgie fancier's lung may be the commonest form of the disease in the United Kingdom due to pet birds kept in homes. Mould contaminating houses may also provoke HP: summer-type HP is common in Japan and due to contamination of the home environment by fungi such as *Trichosporon cutaneum* or *Cryptococcus albidus*. Mould contamination of domestic environments (e.g. cellars,

ultrasonic nebulizers, steam irons, oil heaters, air conditioners) is a less common cause of HP worldwide, but there are many convincing case reports of domestic causes. Composter's lung has been described in relation to inhaling *Aspergillus fumigatus* from a compost heap.

Recreational exposure to antigens occurs in the case of pigeon fancier's lung, where pigeons are kept for the sport of pigeon racing. The widespread nature of provoking antigens is illustrated by examples of the syndrome being attributed to contamination of water by a pullularia fungus in sauna taker's disease (hot tub lung), and the mouthpiece of wind instruments by *Candida albicans* in saxophonist lung and trombone lung.

Farmer's lung

Farmer's lung results from the repeated inhalation of thermophilic actinomycetes from mouldy organic dust such as hay, straw, or crops. When hay is harvested during a wet summer it has a high moisture content of 30–60%, such that it undergoes moulding during storage with proliferation of thermophilic actinomycetes such as *Saccharopolyspora rectivirgula* (formerly *Micropolyspora faeni*) or *Thermoactinomyces vulgaris*. When that hay is then used for feeding cattle or animal bedding during the winter, spores are inhaled, provoking HP. It has been estimated that up to 1.6×10^9 spores may be present in the air after disturbing mouldy hay, and that a farmer working in a confined space, such as a poorly ventilated barn, might inhale 750 000 spores per minute.

The prevalence of farmer's lung varies in different regions from approximately 0.5–5%, and this relates to differences in climate and farming practices in the harvesting, drying, and storage of hay and crops. Farmer's lung as a HP must be distinguished from other diseases such as inhalation fever, silo-filler's lung, and organic dust toxic syndrome, which can arise from the inhalation of endotoxins and other substances on farms.

It can be difficult for patients diagnosed as having farmer's lung to leave their work, and many continue to work on the farm using precautionary measures such as respiratory protection devices and avoidance of situations with high antigen exposures.

In areas of heavy rainfall, the prevalence of farmer's lung can be reduced by improved farming techniques, involving the artificial drying of crops and hay using a blower, better barn ventilation, and the addition of propionic acid to hay to reduce moulding. There have been many changes in the practice of farming over the years, and less than 2% of the population in the United Kingdom now works in agriculture, such that farmer's lung is much less common than previously.

Bird fancier's lung

Bird fancier's lung remains one of the most common forms of HP throughout the world. Although it has been described in people exposed to avian antigens in many different circumstances, it is more common in those exposed to flying birds such as budgies or pigeons, whose feathers are covered by a fine powdery substance called bloom, than in those working with nonflying poultry, such as ducks or turkeys, whose feathers are not well developed and lack bloom. In bird breeder's HP, multiple antigens have been extracted from bird droppings, feathers, serum, egg yolk, egg white, and gut wall. Many of these antigens are dispersed in the air from bloom or droppings and easily inhaled.

In the United Kingdom, pigeons are mainly bred for the sport of pigeon racing, and fanciers typically keep 100–200 pigeons in a loft. The resultant high-intensity intermittent antigen exposure seems to favour the development of acute HP and particularly affects men. By contrast, small numbers of pigeons, typically 1–10, are kept in homes in Mexico as pets, and this chronic low-level antigen exposure is associated with chronic HP progressing to severe lung fibrosis, particularly in women.

In some unusual circumstances, where there is particularly close contact, bird fancier's lung can occur in relation to wild pigeons. Occasionally bird antigens give rise to HP from a hidden source, such as feathered duvets or pillows.

A variety of different lung diseases are associated with bird keeping, including inhalation fevers, asthma, psittacosis (infection with *Chlamydia psittaci*) and HP. Although it is often relatively easy to remove exposure to a pet bird, pigeon fanciers are frequently very committed to their sport and reluctant to stop contact with their pigeons. Many continue to keep pigeons despite a diagnosis of HP, using antigen avoidance and respiratory protection to reduce their level of contact.

Metal-working fluid HP

Metal-working fluids (MWF) are a mixture of water-oil emulsion containing biocides and lubricants which are sprayed onto metal and machines to act as a lubricant and coolant in industries such as car manufacture. The MWF is usually collected and recirculated from a sump or reservoir, and can become contaminated with a variety of bacteria, fungi, and environmental mycobacteria.

Several respiratory diseases may result from the inhalation of the mist of MWF, including lipoid pneumonia, inhalation fevers, asthma, and HP. Several outbreaks of MWF-HP have been reported in metal workers in the United Kingdom, United States, and Europe. Some cases have been attributed to a specific antigen, such as *Mycobacterium immunogenum,* but in other cases workers have demonstrated high IgG levels to a range of bacteria and fungi, hence the precise causative antigen is uncertain and likely to differ between outbreaks depending on the exact circumstances.

The diagnosis of a case of MWF-HP should prompt an inspection of the workplace to review risk management and exposure control, and a survey of other workers who might also be affected. Prevention can be achieved by exhaust-ventilation to reduce the escape of the MWF mist into the air, by monitoring and reducing microbial contamination of the fluid, and sometimes by use of respiratory protection masks by the workers.

Idiopathic HP (no antigen identified)

It is common for CT imaging or lung biopsies to show features suggesting HP in patients attending specialist hospital clinics with interstitial lung disease who have no apparent contact with an antigen or environment known to cause HP. The CT features suggesting HP include centrilobular nodules, mosaic air trapping, and ground-glass shadowing with an upper lobe distribution. Biopsy features suggesting HP include bronchiolocentric distribution of inflammation and fibrosis with poorly formed granulomas.

Up to 30% of patients with CT and biopsy features suggesting HP have no identifiable antigen exposure. Clearly when the potential diagnosis of HP is suggested, a detailed history should be taken from the patient, looking for any potential antigens or environments.

A visit to the patient's home and work environment may identify potential sources of antigens such as mould, humidifiers, or aerosols. It is also common for pigeon fanciers to be reluctant to inform doctors that they keep pigeons, because of a perception that doctors disapprove of the sport.

It may be useful to measure antibody responses to avian antigens, Aspergillus, and thermophilic actinomycetes to detect evidence of unrecognized exposure to these antigens. Some cases of idiopathic HP have subsequently been attributed to previously undetected contact with avian antigens from feathers in duvets or pillows. Measurement of auto-antibodies may provide clues to alternative diagnoses such as interstitial lung disease associated with connective tissue disease.

The lack of an identifiable antigen casts doubt on the provoking factors and mechanisms of disease in cases of idiopathic HP, and it is important to realize that HP is not fundamentally a histopathological or radiological diagnosis, but rather a clinical syndrome. The histopathology describes the pattern of disease rather than the precise causation.

Patients with idiopathic HP (no antigen identified) appear to have a worse prognosis than patients with HP and an identifiable antigen. It is possible that failing to identify an antigen perpetuates exposure that drives disease progression. It is also possible that patients classified as having idiopathic HP may have a disease process driven by other mechanisms, and there is sometimes difficulty in differentiating HP from other diseases such as nonspecific interstitial pneumonia, idiopathic pulmonary fibrosis, airways centred fibrosis, and connective tissue disease. In practice, patients classified as having idiopathic HP (no antigen identified) are usually given trials of treatment with corticosteroids and other immunosuppressive agents, but there is some evidence that their response to treatment is poorer than those in whom an antigen has been identified.

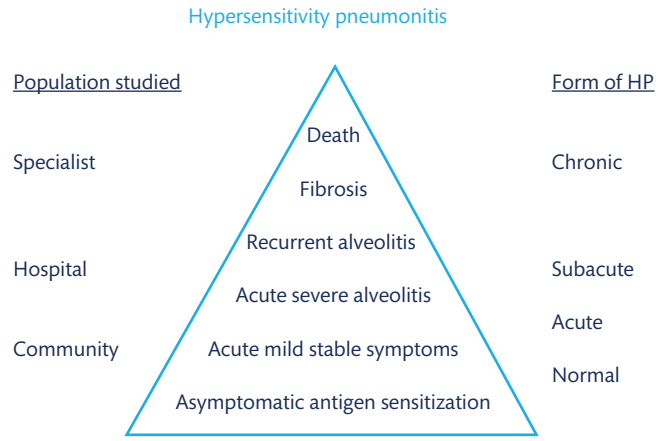

Fig. 18.14.4.1 Hypersensitivity pneumonitis is a heterogeneous dynamic clinic syndrome which varies in its initial presentation and clinical course. Traditionally the disease is classified into acute, subacute, and chronic forms. The clinical features depend on the population studied. Community-based studies often identify subjects with mild intermittent acute symptoms, and subjects who have an immune response to the antigen but who have not developed disease. In hospital practice, patients may present acutely with severe alveolitis. Studies from specialist interstitial lung disease services tend to have selected populations of patients who have developed chronic disease with progressive fibrosis.

Epidemiology

The epidemiology of HP is difficult to define because of the diverse circumstances in which the disease occurs, the complex dynamic nature of the clinical syndromes, and the different forms of the disease. Very different patterns of disease are seen when studies are undertaken at community level in patients at home, in workplace-based outbreaks, in primary care, or in specialist hospital settings (Fig. 18.14.4.1).

Prevalence rates vary widely between countries and are influenced by factors such as climate, local customs, smoking habits, and different work practices and processes. The most common types of HP in several series are bird fancier's lung from a pet bird in the home or the sport of pigeon racing, farmer's lung due to fungi in mouldy hay or straw, and various types of humidifier lung due to fungi or bacteria in water aerosols in the home or workplace. A study by the international HP research group showed that 61% of cases were due to birds, 21% to farming, and 12% to various fungi encountered in the home or workplace.

In the United Kingdom it is estimated that 1 million homes have a pet bird, 2% of the population work in agriculture, and there are approximately 43 000 registered pigeon fanciers. Only a small percentage of those of those exposed to an antigen of HP develop the disease. It is estimated that 3.4% of budgie fanciers, 10–15% of pigeon fanciers and up to 5% of farmers develop HP. A study of primary care data in the United Kingdom estimated that there were about 600 new cases of HP in the United Kingdom each year, giving an incidence of HP of 1 per 100 000 person-years with a mean age of diagnosis of 51 years.

HP accounts for only about 6% of occupational lung disease reported to the United Kingdom surveillance scheme, of which almost 50% of reported cases involved farmers or farm workers, followed by 15% affecting workers in material, metal, or electrical processing trades. However, in recent years there has been a change, with metal-working fluid HP becoming the most commonly reported cause of occupational HP. In reported outbreaks of humidifier lung in offices and factories in North America the prevalence rates among workers have varied from 15 to 70%. The risk of developing HP from metal-working fluids varies substantially according to the degree and nature of microbial contamination, and the ease with which aerosols of the fluids are released into the working environment. Up to one-third of workers have been affected in some outbreaks.

Smaller numbers of people are employed making whisky from germinating barley (maltings), raising mushrooms on a variety of antigenic composts, or handling bagasse (the fibrous stem that remains when sugar is extracted from sugar cane), but within some of these populations HP was a common problem until excessive exposure levels were controlled. In Japan, the seasonal summer growth of *T. cutaneum* in the home is a common cause of HP.

Pathogenesis

Antigens of HP

The antigens which provoke HP have important characteristics that distinguish them from the antigens that provoke asthma.

These characteristics include their size, solubility, particulate nature, and their capacity to provoke a nonspecific inflammatory response and a specific immune reaction. They are usually small, with a particle size less than 3 μm in diameter, such that they can be inhaled into the distal bronchial tree and alveoli, where they are cleared via local lymphatics to the hilar nodes, which seems to be important in producing IgG antibody responses. By contrast, antigens more typically associated with asthma are larger at about 30 μm in diameter, and are preferentially deposited in the proximal airways, where they tend to provoke an IgE antibody response in atopic subjects. The antigens of HP have powerful adjuvant properties, with a capacity to activate complement by the alternative pathway, to stimulate macrophages, and to enhance delayed cellular responses, with the release of interleukin (IL)-1 and tumour necrosis factor (TNF)α.

Susceptibility and environmental factors

Individual susceptibility is important in determining the immune response: less than 10% of subjects repeatedly exposed to antigens of HP develop the disease. Host risk factors are poorly understood. Several studies have suggested links between HLA types and HP, with an increased occurrence of HLA DR7 in pigeon fancier's lung in a Mexican population, HLA B8 in farmer's lung and pigeon fancier's lung in Caucasians, and HLA-DQw3 in Japanese summer-type HP, but other studies have found no association. Genetic factors are known to influence immune response. Gene polymorphisms resulting in high-responders for TNFα result in a greater risk for developing HP. Similarly, animal models of HP suggest that multigenic factors are important in determining the susceptibility of certain strains of mice to the development of granulomatous inflammation.

Environmental factors, including antigen concentration, duration, and frequency of exposure, particulate size, antigen solubility, and variability in work practices may influence the prevalence, severity, and course of HP. It has been repeatedly shown that HP is less common in current smokers, and smoking reduces the IgG response to inhaled antigens, influences cytokine production and impairs macrophage function. Smoking may also reduce the risk for other T-cell-mediated immunological disorders such as sarcoidosis, ulcerative colitis, and some types of occupational asthma. The key cell in a complex series of interactions is probably the alveolar macrophage, which is critical in presenting antigen to CD4+ T lymphocytes and so to activating cellular immune mechanisms. Although smoking increases macrophage numbers and their metabolic activity, the activated cells show impairment of both the expression of surface major histocompatibility (MHC) class 2 antigens and the production or release of IL-1 and inflammatory mediators derived from arachidonic acid metabolism (leukotriene B_4, prostaglandin E_2, thromboxane B_2). It is also argued that the increased macrophage numbers down-regulate pulmonary immune responses in a purely nonspecific fashion by impairing antigen access to more effective blood monocytes.

There is some evidence that the onset of HP may be precipitated by additional nonspecific lung inflammation. Respiratory viruses, such as influenza A, are commonly detectable by the polymerase chain reaction in the lower airways of patients presenting with acute HP, and in a mouse model of HP it has been shown that Sendai virus infection enhances the lung response to antigenic challenge with *Saccharopolyspora rectivirgula*. Other animal models of HP require the induction of nonspecific lung inflammation by adjuvants such as Bacille Calmette–Guérin (BCG) or carrageenan, before HP can be provoked by antigen challenge.

Immunopathogenesis

The immunopathogenesis of HP is complex and incompletely understood. Patients have high levels of antigen exposure and demonstrate complex immune responses involving antibody and cellular immune mechanisms. An outline of the possible immunopathology of HP is illustrated in **Figs. 18.14.4.2** and **18.14.4.3**, and it is likely that different mechanisms are important at different stages of the process, depending on whether the patient is presenting with acute HP, chronic HP, or progressive pulmonary fibrosis.

Initially it was thought that HP was an immune complex-mediated disease, but greater emphasis has subsequently been placed on the role of cellular immune responses. The evidence for deposition of immune complexes is not convincing, and neither IgG nor IgM antibodies are uniformly demonstrated in the sera of affected subjects unless sensitive detection techniques such as the enzyme-linked immunosorbent assay (ELISA) or radioimmunoassays are used. More importantly, these antibodies are frequently found in subjects who are similarly exposed but clinically unaffected. A closer association of disease with the IgG4 antibody subclass has been suggested, but the significance of this is not yet apparent. It is clear, however, that vasculitis—a cardinal feature of the experimental Arthus reaction—is not a characteristic feature.

The inflammatory reaction is dominantly lymphocytic or mononuclear rather than polymorphonuclear, although a transitory polymorphonuclear leucocyte response is typical immediately following exposure. In experimental animal models of HP, the disease cannot be induced by the passive transfer of hyperimmune serum, but transfer of specifically sensitized lymph node cells intraperitoneally followed by antigen challenge produces lesions closely resembling those seen in HP. Immediately after antigen challenge there is an influx of neutrophils into the alveoli. This may be stimulated by the formation of immune complexes and direct activation of

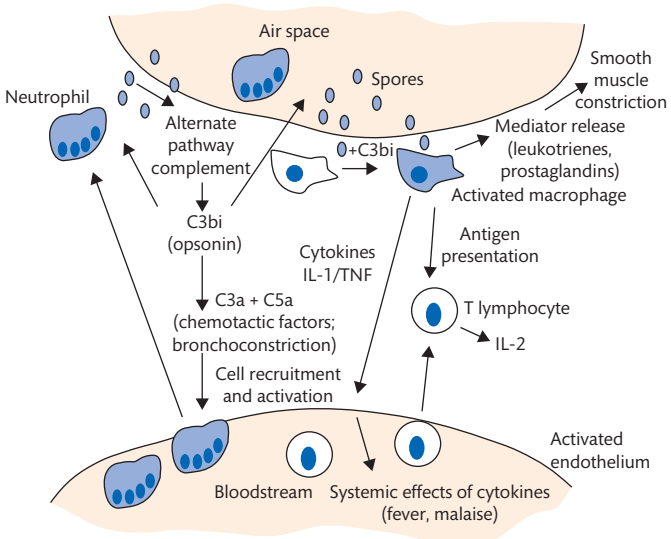

Fig. 18.14.4.2 Possible immunopathogenesis: acute phase.

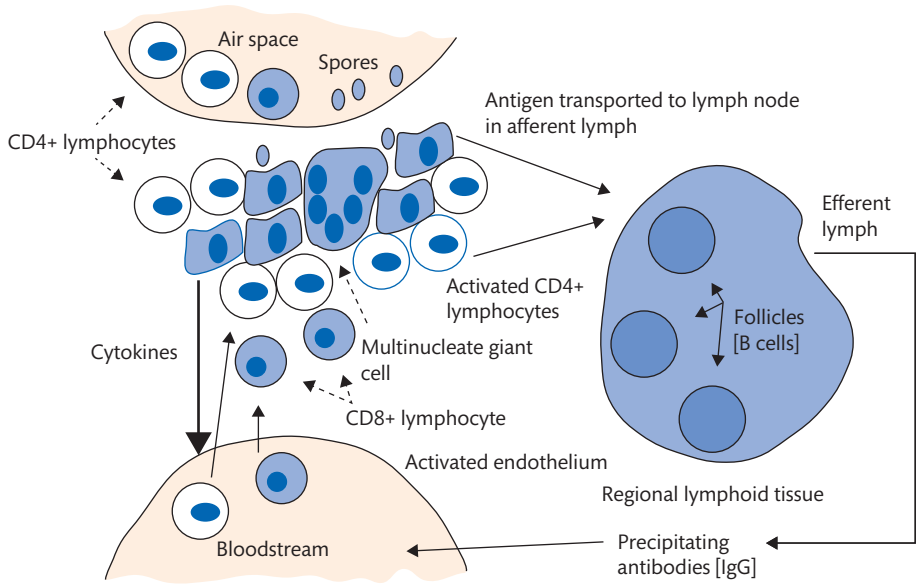

Fig. 18.14.4.3 Possible immunopathogenesis: subacute/chronic phase.

complement by the alternative pathway. This neutrophilic alveolitis is transient and is followed by the influx of activated T-cells with a preponderance of CD8 T-cells. As time passes from antigen exposure, the number of CD8 cells decreases and there is an increase in CD4 T-cells. Alveolar macrophages are activated and an array of pro-inflammatory cytokines such as tumour necrosis factor (TNF)-α, interleukin (IL)-6, IL-17 and interferon (IFN)-γ is produced. Regulatory cytokines such as IL-10 are also secreted and may play a role in damping down the inflammatory response. Toll-like receptors (TLR) may also be involved. These recognize particular bacterial and fungal lipoproteins. TLR2 and TLR9 appear to be important in the initial response.

The factors governing granulomatous inflammation are uncertain, but animal models of schistosome-induced granulomatous inflammation show that certain factors, such as T-suppressor effector factor and cyclo-oxygenase products, inhibit macrophage expression and granuloma formation, whereas other factors such as lipoxygenase products enhance granuloma formation. There are therefore certain modulating factors which may enhance or suppress the disease process at various stages.

Bronchoalveolar lavage in subjects exposed to HP antigens has shown excess numbers of T lymphocytes, whether they were clinically affected or not, although the proportions of T-cell subpopulations have varied according to disease activity and the circumstances of exposure. It is known that different antigenic determinants from a given inducing microbial source may lead to different immunological responses, and it seems likely that cytotoxic activity and released cytokines (e.g. IL-6 and TNFα) play some role, possibly by activating the vascular endothelium and thereby recruiting and activating further macrophages and inflammatory cells. In experimental models IFN-γ has been shown to play a major role (an excess of IFN-γ-producing T-cells is present in the lungs), and IL-10 ameliorates the disease. Other studies implicate IL-6, IL-8, IL-12, IL-17, IL-18, and IL-22, monocyte chemotactic protein-1 (MCP-1), intercellular adhesion molecule 1 (ICAM-1), mast cells, and NK cells.

Cytokines, possibly together with anaphylatoxins from the degradation of complement components (C4, C3, C5), are likely to be responsible for the systemic influenza-like symptoms that are so characteristic of the acute form of HP. These symptoms are indistinguishable from those of grain fever in grain workers, 'Monday fever' in cotton workers, humidifier fever in subjects exposed to contaminated humidifiers, and metal fume fever in welders. In these situations the febrile disorder is not characteristically associated with clinical alveolitis, raising the possibility that its occurrence with the acute form of HP is an independent phenomenon, rather than an integral part of the disease progression. In favour of this hypothesis has been the finding of high levels of endotoxin from Gram-negative bacteria (which are known to provoke these symptoms) in grain dust, cotton dust, contaminated humidifiers, and many of the 'mouldy' vegetable dusts that cause HP.

Pulmonary fibrosis may represent a common pathway for many interstitial lung diseases. The precise links between inflammation and fibrosis in interstitial lung disease are also poorly understood, but may relate to the extent of injury to epithelial cells and basement membrane, and factors governing fibroblast activation, collagen deposition, and collagen degradation. The onset of fibrosis is associated with a poor response to treatment and increased mortality. The mechanisms for profibrotic and antifibrotic regulation by various cytokines and cell surface markers are uncertain. In advanced fibrotic disease it is often difficult to differentiate HP from idiopathic pulmonary fibrosis. However, there are different gene expression signatures in these diseases. In HP, the gene expression signature on oligonucleotide arrays are is of those functionally associated with inflammation, T-cell activation, and immune responses, whereas idiopathic pulmonary fibrosis is characterized by the expression of tissue remodelling, and epithelial and myofibroblast genes.

In summary, the immune mechanisms underlying HP are complex and may differ at different stages of the disease. This diversity is reflected in a dynamic heterogeneous clinical syndrome which varies greatly in its initial presentation and subsequent clinical course.

Clinical features

The clinical features of the disease depend greatly on the population studied, the clinical circumstances of antigen exposure, and the pattern of the disease in an individual patient. The clinical spectrum varies from mild recurrent symptoms, often managed by patients themselves at community level, to acute severe pneumonitis presenting to hospital, and to progressive fibrotic lung disease in patients seen in specialist interstitial lung disease clinics.

Traditionally HP is classified into acute, subacute, and chronic forms, although patients do not always fit neatly into this classification, and different patterns emerge over time.

Acute hypersensitivity pneumonitis

Acute HP is characterized by recurrent episodes of breathlessness, cough, fevers, malaise, and flu-like symptoms, occurring 4–8 hours after antigen exposure. Lung function tests, chest radiographs, and CT images may be abnormal after exposure but usually return to normal between episodes. Characteristically there is a latency period, which may vary from weeks to years, during which there are no symptoms, as sensitization to the antigen develops before the onset of disease.

The severity and duration of symptoms depend critically on exposure dose and individual susceptibility. With low levels of acute exposure, symptoms are mild and persist for a few hours only. When occupation is responsible, the affected worker may feel unwell only at home during the following evening or night, and be fully recovered by the next morning, such that the relevance of the workplace environment may not be initially obvious.

In hospital practice, patients may present acutely with severe HP with fever, breathlessness, hypoxia, and diffuse shadowing on a chest radiograph or CT. Initially these patients may be suspected to have developed infective pneumonia and may receive antibiotics. The symptoms may resolve as admission to hospital removes them from further antigenic contact, but they may present again with recurrent episodes. It is crucial to ask about potential antigenic exposure to identify the correct diagnosis in such cases.

Chronic hypersensitivity pneumonitis

Chronic HP is characterized by the insidious development of breathlessness and persistent pneumonitis. It is typically seen in a person who keeps a single budgie in the home. The level of antigenic exposure to avian dust is comparatively small compared with that of the farm worker forking bales of heavily contaminated hay in a poorly ventilated barn, but it is encountered almost continuously, particularly if the affected individual is housebound.

Subacute hypersensitivity pneumonitis

In subacute HP patients may demonstrate chronic pneumonitis with episodes of acute symptoms after antigen exposure.

Diagnostic criteria and investigation

No single clinical feature or laboratory test is diagnostic of HP, and the diagnosis is made from a combination of characteristic clinical features, radiographic abnormalities, lung function tests, immunological tests and (in some cases) lung biopsy, and the exclusion of alternative disease processes.

The diagnostic approach should be adapted to the circumstances of the clinical problem, and very few patients will demonstrate all features of the disease at any one point in time. In many cases the diagnosis can be established from clinical features supported by chest radiography, CT, serology, and lung function tests. In those with lung fibrosis the difficulty is in differentiating chronic HP from idiopathic pulmonary fibrosis, and invasive tests such as bronchoalveolar lavage, lung biopsy, and antigen challenge tests may be appropriate.

Suspicion of an association between symptoms and contact with a provoking antigen is a key step in the diagnostic process. In the acute form of HP this association may be readily apparent. In the chronic form symptoms often do not show a temporal relationship to antigen exposure, and sometimes no antigenic source is apparent. An important step is the demonstration of either an antibody or cellular immune response to the provoking antigen. However, this merely confirms that that the patient has had a sufficient level of exposure to the antigen to develop sensitization, and this is not sufficient to establish a diagnosis of HP, since many asymptomatic subjects show similar antibody or cellular responses. Serological tests for antibodies to avian antigens, thermophilic actinomycetes, and Aspergillus may be useful in identifying exposure to a relevant antigen.

Radiological imaging

With the acute form of the disease the chest radiograph commonly shows no abnormality between episodes. When the radiograph is abnormal, there is a widespread ground-glass appearance or an alveolar filling pattern, particularly in the lower and mid-zones. This may resolve within 24–48 h once exposure has ceased. In more subacute forms small reticular opacities may persist for several weeks despite cessation of exposure. Occasionally a more nodular pattern occurs. In practice, the radiographic appearances vary considerably from patient to patient and correlate poorly with the clinical severity of the disease.

High-resolution CT is more sensitive than chest radiography in demonstrating parenchymal changes. The typical features are diffuse bilateral ground-glass attenuation with small centrilobular nodules with a mid and lower zone distribution. A characteristic finding is of a mosaic pattern due to focal areas of air trapping, often with a clear lobular distribution, within diffuse areas of ground-glass attenuation. The extent of air-trapping on expiratory CT correlates with an increase in residual volume on pulmonary function tests. In more advanced chronic HP, the CT findings are of pulmonary fibrosis with linear opacities, architectural distortion, and honeycombing, often indistinguishable from other causes of pulmonary fibrosis. Features which suggest HP rather than idiopathic pulmonary fibrosis include a relative sparing of the lung bases, lack of peripheral subpleural distribution of fibrosis and the presence of centrilobular nodules (Fig. 18.14.4.4). Lymph node enlargement and/or pleural involvement are not characteristic.

Lung function studies

The results of lung function studies vary according to severity of the disease and the interval to last antigen exposure. When lung function is impaired, the pattern suggests parenchymal and interstitial disease,

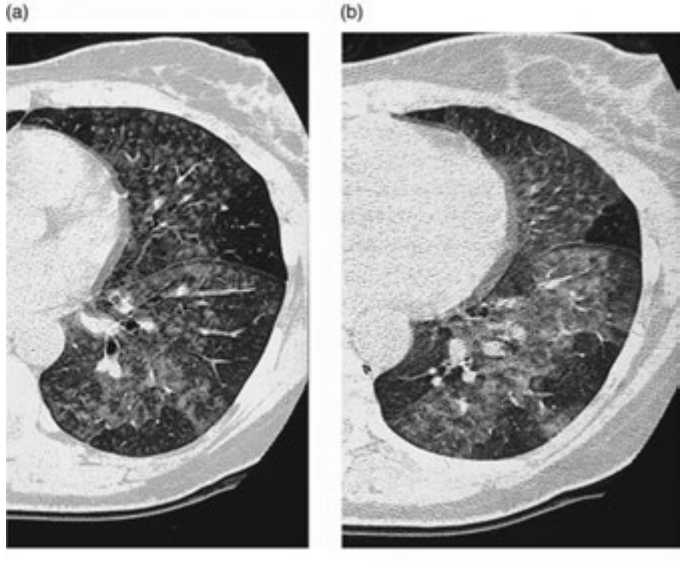

Fig. 18.14.4.4 (a) CT scan of a woman aged 44 years who had never smoked whose lung biopsy showed the typical appearances of subacute HP. She kept two budgies in her home and had serum precipitins to avian antigens. The scan shows marked ground-glass attenuation of the lung parenchyma, which is nodular in some areas due to characteristic peribronchiolar (and centrilobular) foci. In other areas there is increased translucency because of bronchiolar obstruction and air trapping. Both the ground-glass attenuation and the increases in translucency are exaggerated in the expiratory film (b), giving a 'mosaic' pattern. She recovered fully after the birds left her home.

but is otherwise nonspecific. There is a restrictive defect with reduced lung volumes and impaired carbon monoxide gas transfer (diminished *TL*co and *K*co), decreased compliance, and in more severe cases arterial hypoxaemia. Although total lung capacity is reduced, residual volume is often increased, suggesting air trapping as a result of bronchiolar involvement. Occasionally there is also evidence of obstruction of the large and peripheral airways. Serial measurements of lung function may be particularly useful in demonstrating that impairment is closely related to the relevant exposure.

Bronchoalveolar lavage

Bronchoalveolar lavage characteristically shows a lymphocytic alveolitis with a predominance of CD8 T-cells, but the cell profile is dependent upon the interval from last antigen exposure. A neutrophilic alveolitis is seen immediately after antigen challenge and the number of CD8 T-cells falls after cessation of antigen contact. A lymphocytic alveolitis is seen in asymptomatic subjects exposed to an antigen and in patients with organic dust toxic syndrome. Sarcoidosis is also characterized by lymphocytosis in bronchoalveolar lavage fluid, but B-lymphocyte numbers are decreased and the excess T lymphocytes are typically CD4 + helper cells, with the CD4 + to CD8 + ratio normally exceeding 1. By contrast, the ratio is typically reversed in HP, CD8 + cells outnumbering CD4 + cells, and B-lymphocyte numbers are not decreased. Lymphocyte markers may therefore help distinguish sarcoidosis from HP.

Lung biopsy

Lung biopsy typically shows lymphocytic infiltration, foamy macrophages, poorly formed granulomas, and bronchiolitis, but this depends on the stage of the disease and in more advanced disease the predominant feature may be pulmonary fibrosis resembling usual interstitial pneumonia of idiopathic pulmonary fibrosis. Close correlation with all the clinical details is required to differentiate the granulomatous inflammation of HP from other disease processes such as sarcoidosis.

There has been little opportunity to characterize the pathology of the acute form of HP histologically because biopsies are very rarely taken within 24–48 h of a provoking exposure. Initially there is a nonspecific diffuse pneumonitis with inflammatory cellular infiltration of the bronchioles, alveoli, and interstitium, accompanied by oedema and luminal exudation.

With ongoing exposure, whether continuous or intermittent, the more familiar appearances of the subacute forms of HP evolve. The typical histological appearance of subacute HP is illustrated in Fig. 18.14.4.5. The most characteristic feature is the formation of epithelioid noncaseating granulomas. These are generally less well formed than in sarcoidosis, less profuse, and often evanescent. They can be recognized within 3 weeks of the initiating exposure, and generally resolve within 6–12 months. In parallel, fibrosis evolves alongside cellular infiltration of the interstitium with histiocytes, lymphocytes, and plasma cells. Macrophages with foamy cytoplasm may be prominent in the alveolar spaces, and organization of the inflammatory exudate may lead to intra-alveolar fibrosis. Obstruction or obliteration of bronchioles is common. Foreign-body giant cells may reflect the dependence of HP on antigens derived from inhaled foreign material, as does a peribronchial predominance of the inflammatory response. Vasculitis is notable by its absence.

Immunological tests

The demonstration of a serum IgG antibody response to the inducing organic dust is the most widely used method of confirming an immune response to an inhaled antigen. Although affected subjects tend to have higher antibody levels than those who are exposed but unaffected, the antibody response tends to correlate more closely with exposure than with disease. If the more sensitive ELISA is used, rather than the traditional Ouchterlony double-gel diffusion test, even higher rates of false-positive results are obtained.

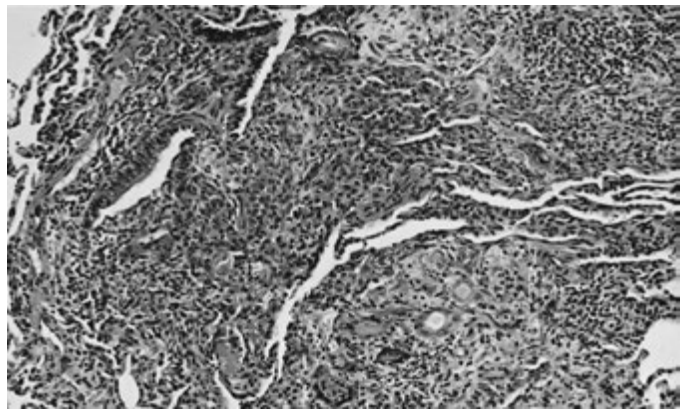

Fig. 18.14.4.5 Histological appearance: subacute disease. There is bronchocentric interstitial fibrosis and chronic inflammation, with poorly formed interstitial granulomas including giant cells. (Haematoxylin and eosin stain at medium magnification.)
Courtesy of Dr T. Ashcroft.

In practice, the absence of an IgG precipitin response is uncommon in subjects eventually proven to have HP. This is of considerable value in that a negative test generally makes the diagnosis unlikely.

The proliferative response of peripheral blood lymphocytes to specific antigens has been used in some research studies as a measure of a cellular immune response in establishing a diagnosis of HP in patients with interstitial lung disease, but these tests are not widely available and their sensitivity and specificity for diagnosing HP are not established.

Challenge tests

When the diagnosis remains in doubt, some form of inhalation challenge test may be necessary. The simplest method involves comparison of experimental periods spent away from the suspected causative environment with similar periods of continuing exposure. This can be done in workplace-based settings or in the setting of a pigeon loft, for example, where subjects undertake their usually activities, with monitoring of symptoms, clinical signs, and lung function. The acute form of the disease is likely to be recognized in this way.

When a definitive diagnosis is particularly important, laboratory-based inhalation challenge tests can be used. These employ a variety of techniques, ranging from nebulizing soluble extracts to recreating natural environmental exposures in an exposure chamber. However, the use of such inhalational challenge studies in the diagnosis of HP has been hampered by the lack of standardized antigens, the diversity of the clinical manifestations of the disease, and the difficulties in defining objective criteria that characterize a positive test. The influenza-like component of positive reactions is often uncomfortable, and if excessive doses are administered these tests can be hazardous. Furthermore, objective evidence for positive reactions may be difficult to obtain from conventional lung function tests.

Table 18.14.4.2 outlines the sensitivity and specificity of certain parameters from a study of 144 inhalation challenge tests. Together they provide high specificity and high sensitivity. Auscultation, chest radiography, measurements of gas transfer, and arterial blood gas analyses are often too insensitive to provide useful diagnostic information.

Table 18.14.4.2 Diagnostic features of positive inhalation challenge tests

Diagnostic changes within 36 h of challenge exposure	Sensitivity (%)
Increase in body temperature to >37.2°C	78
Increase in circulating neutrophils by ≥2.5 × 10^9/litre	68
Decrease in circulating lymphocytes by ≥0.5 × 10^9/litre, with lymphopenia (<1.5 × 10^9/litre)	52
Decrease in forced vital capacity by ≥15%	48
Increase in exercise minute volume by ≥15%	85
Increase in exercise respiratory frequency by ≥25%	64

The data were taken from a series of 144 antigen and control challenge tests in 31 subjects. Diagnostic endpoints were chosen to produce specificities of approximately 95% after mean changes associated with positive challenge tests were shown to be highly significant. When each monitoring parameter was given a score of 1 for a significant result, a total score of 2/6 or more was associated with a specificity of 100% and a sensitivity of 78% for the 144 challenge tests.

Differential diagnosis

The differential diagnoses to be considered depend on the population studied and the circumstances of the disease. The acute form of HP needs to be distinguished from organic dust toxic syndrome and mere sensitization to the antigen. The chronic fibrotic form may mimic idiopathic pulmonary fibrosis or nonspecific interstitial pneumonia.

Organic dust toxic syndrome

Systemic influenza-like symptoms and respiratory distress may also follow an unusually heavy exposure to contaminated vegetable produce. In 1986 an international symposium considered a further disorder that occurs within hours of heavy respiratory exposure to dusts containing fungal toxins, especially those released on decapping silos.

The condition typically occurs after a single exposure to an unusually high level of organic dust, and may arise in subjects who have not had previous exposure. All subjects that have a similar degree of exposure develop a similar clinical illness. It is the result of direct toxicity rather than hypersensitivity, and the term 'organic dust toxic syndrome' was recommended to describe it.

Its effects are usually mild and self-limiting, but severe respiratory embarrassment can occur. Not only does organic dust toxic syndrome occur in circumstances which favour the occurrence of HP (particularly silos and swine/poultry confinement buildings), but its clinical features have much in common with HP, and to a lesser extent with nitrogen dioxide toxicity, which may also affect silo workers (Table 18.14.4.3).

Most organic dusts contain an array of bacteria, fungi, and endotoxins, which can give rise to this direct toxic lung inflammation. These are sometimes associated with systemic febrile reactions without impairment of lung function, as in the case of farmer's fever, grain fever, swine fever, and humidifier fever. These patients do not usually have antibodies to relevant antigens.

Nitrogen dioxide toxicity

In the agricultural silo, decomposing grain or silage releases nitrogen dioxide into the confined space immediately above the level of the stored produce. Since this is denser than air it disperses slowly and may reach sufficiently high concentrations to cause asphyxia. Silo-fillers lung is a toxic pneumonitis resulting from inhalation of nitrogen dioxide. It can produce severe pneumonitis with pulmonary oedema and death.

Treatment and prognosis

Antigen avoidance

Removal of exposure to the provoking antigen is the key treatment for patients with HP, and complete cessation of contact is the safest advice for these patients. In patients with the acute form of HP cessation of antigenic exposure usually results in rapid resolution of the disease. In patients admitted to hospital with more severe acute pneumonitis there is often an apparent beneficial response to corticosteroids, although it is difficult to distinguish between the effects of treatment and the effects of antigen avoidance brought about by the admission to hospital.

Table 18.14.4.3 Characteristics of nitrogen dioxide toxicity (silo-filler's disease), organic dust toxic syndrome, and acute farmer's lung

	Nitrogen dioxide toxicity	Organic dust toxic syndrome	Acute farmer's lung
Susceptibility in smokers	Unknown	Unknown	Decreased
Relation to time of harvest	Days	Months to years	Months to years
Microbial decomposition of harvest product	Little	Marked	Variable
Confined exposure space	+++	+	+
Previous episodes	–	+	++
Symptoms			
Dry cough	++	++	++
Breathlessness	++	++	++
Wheeze	–	–	–
Systemic upset	+	+	++
Signs			
Basal crackles	+	+	+
Fever	+	+	+
Time of onset after beginning exposure	1–10 h	1–10 h	1–10 h
Duration	Hours to days	Hours to days	Hours to days
Investigations			
Leucocytosis	+	+	+
Radiograph–small irregular opacities, alveolar shadows	+	±	+
Restricted ventilation	+	±	+
Reduced gas transfer	+	±	+
Hypoxaemia	+	±	+
Fungi from secretions/biopsy	–	++	+
Methaemoglobinaemia	+	–	–
Serum precipitins	–	–	+ (?– in smokers)
Response to steroids	+	–	++
Life-threatening	Not uncommonly	Rarely	Rarely

Some patients have had mild stable symptoms for several years, but have not consulted doctors because they fear that their livelihood is at stake in the case of farmers, or that their commitment to their sport will not be appreciated in the case of pigeon fanciers. Sometimes it is unrealistic for the affected individual to change the relevant working, domestic, or recreational environment completely, and many such patients continue some exposure, and surprisingly this does not inevitably result in progressive disease.

Many patients will have adopted strategies to reduce antigen exposure, and further advice can be given in that regard. For example, pigeon fanciers can be encouraged to spend less time in the loft, to avoid activities where there is a high level of antigen, such as 'scraping out', and to wear a loft coat and hat that are removed on leaving the loft so as to avoid continuing contact with antigen carried on clothing or in hair. In particular, pigeon fanciers should be specifically advised not to transport pigeons on the back seat of their car, as this can result in intense exposure in a confined space.

Farmers can use silage rather than hay for feeding animals, and can adopt modern practices with drying systems which reduce the moisture and mould content of hay. An alternative is some form of 'pickling', so that the produce is preserved chemically. With silage, for example, newly cut grass is kept under impervious covering in relatively sealed conditions. Initial enzymatic and moulding processes use up available oxygen, and produce aldehydes and other preservative chemicals. These create nearly anaerobic conditions and protect the produce until it is used. Similarly, hay may be sealed in plastic bags, or grain or bagasse may be treated with propionic acid.

Occupational aspects

Where outbreaks of HP occur in workplaces, it is important that an industrial hygienist and occupational physician work with the management and employees to identify the process involved and to reduce or remove the risk to the affected individual and fellow workers. If workers suffer disability or have to stop work because of occupational HP, they are entitled to compensation either through governmental compensation schemes or through pursuit of a legal claim via the civil courts. Sometimes, as in the case of contaminated metal-working fluid or a humidifier system, the source of the antigen can be identified and removed.

Assessment and surveillance of other workers is important as often they may have been affected but not diagnosed correctly. The affected individuals who continue to work in the occupation responsible for their disease can often reduce their exposure substantially by changing the pattern of their particular duties, or working in

different areas of the factory. Modifications can always be made to the environment to lessen the level of exposure, but their extent will be limited by expense and should be justified by need. When ventilation and humidification systems are themselves responsible for HP, major mechanical alterations may be necessary, and the methods of humidification and temperature control may need to be changed. The crucial need is to reduce the ease with which normal airborne microbial contaminants are able to proliferate in stagnant, reservoir, collections of water. For this there may be a role for 'biocide' sterilizing agents, but these are also likely to become airborne and respirable and so must have low intrinsic toxicity and sensitizing potency. Respiratory protection masks have been shown to improve symptoms and prevent a reaction to an antigen challenge, but these have to be of sufficient quality to filter out small particles of respirable dust, and they have to be worn regularly and have a close fit to the face to prevent antigens being inhaled.

Continued exposure

Where a patient with HP decides to continue exposure to the antigen, there is a risk of recurrent episodes of acute HP and sometimes progression of the disease to lung fibrosis. Complete cessation of antigen exposure remains the safest advice, but where this is not possible methods to reduce the level of antigen exposure should be recommended, and measuring the level of circulating antibody to the antigen may be a useful guide to the effectiveness of avoidance measures. Ongoing medical supervision of symptoms, lung function, and chest radiographs is advisable.

Surprisingly, acute HP does not usually progress to chronic fibrotic disease, even when there is continued antigen exposure. A long-term follow-up study of 92 farm workers presenting with acute farmer's lung showed that while most continued to live on farms, only some developed radiographic evidence of pulmonary fibrosis (39%) or impairment of carbon monoxide gas transfer (30%), but 28% gave histories of chronic productive cough and 25% had airway obstruction. A similar 10-year outcome has been reported in pigeon fanciers with acute HP; again, most elected to continue their antigenic exposures despite medical advice to the contrary, but symptoms tended to improve and only a few had residual abnormalities on chest radiographs or lung function tests. Some patients seem to remain in a state of equilibrium with the antigen over long periods of time without developing progressive disease. This intriguing phenomenon has also been reported in animal models of the disease, where repeated antigen challenges result in a waning of the immune response rather than progression of the disease. The interaction of the antigen and the host response in HP is complex, and it is clear that there are several factors which modulate the response. This also suggests that the underlying pathogenic mechanisms differ between acute HP and chronic fibrotic disease.

Acute severe alveolitis

Patients presenting to hospital with acute severe alveolitis are usually treated with corticosteroids. A randomized, double-blind, placebo-controlled study of corticosteroids in patients with acute farmer's lung showed more rapid improvement in lung function, with a significantly higher transfer factor for carbon monoxide (*TL*co) and transfer coefficient (*K*co) at one month compared to the control group, but there was no difference in the long-term outcome between the two groups.

Chronic fibrotic hypersensitivity pneumonitis

Patients with chronic fibrotic HP have severe disease which is often progressive, and it is essential for these patients to avoid further contact with the provoking antigen. Sometimes this fibrotic form of HP progresses even after cessation of antigen exposure, suggesting that the disease mechanisms giving rise to fibrosis may be progressive and not dependent on ongoing antigenic stimulation. Many of these patients improve on corticosteroids, particularly where a lung biopsy shows a nonspecific pneumonia or cryptogenic organizing pneumonia pattern of disease rather than a usual interstitial pneumonia pattern. Evidence of lung fibrosis on biopsy or CT imaging is an adverse feature and is associated with a high likelihood of progressive disease and death from respiratory failure. Some of these patients show a similar pattern of disease progression as is seen in idiopathic pulmonary fibrosis.

Acute exacerbations of chronic HP may also occur, and are characterized by an acute deterioration in breathlessness, oxygenation, and lung function. As is the case with acute exacerbations of idiopathic pulmonary fibrosis, these patents are usually treated by corticosteroids during exacerbations. Where patients fail to respond to corticosteroids other immunosuppressive drugs, such as azathioprine, cyclophosphamide, or mycophenolate, are often tried, but evidence of benefit is based on case reports rather than formal clinical trials. Rituximab, a B-cell depleting anti-CD20 antibody, has also been reported to have a beneficial effect, suggesting an immunopathogenic role for B cells in some patients with severe HP.

Lung transplantation may be necessary in patients with progressive HP who have failed to respond to antigen avoidance and immunosuppressive treatments. Although patients with HP have an exaggerated immune response to certain inhaled antigens, they have lower rates of acute rejection of transplanted lungs and a better prognosis than patients with idiopathic pulmonary fibrosis. There have been reports of recurrence of the disease in the transplanted lungs if there is re-exposure to the antigen.

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18.14.5 Pulmonary Langerhans' cell histiocytosis

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ESSENTIALS

Pulmonary Langerhans' cell histiocytosis is characterized by a reactive monoclonal proliferation of activated histiocytes in the distal bronchioles. It presents with cough, breathlessness and (sometimes) systemic symptoms. Chest radiography and CT typically show nodules which then cavitate and may rupture, causing pneumothorax. Corticosteroids and/or cytotoxic drugs are of some benefit, and lung transplantation is an option for progressive disease.

Introduction

Pulmonary Langerhans' cell histiocytosis (LCH) is a rare disease characterized by a reactive monoclonal proliferation of activated histiocytes in the distal bronchioles, resulting in inflammatory nodules, cyst formation, and fibrosis. Langerhans' cells are a particular type of histiocyte derived from dendritic cells in the bone marrow. They normally migrate in the blood to the squamous epithelium of the skin, lungs, gastrointestinal, and female genital tract, where they are involved in antigen presentation to T cells. Abnormal proliferation of histiocytes is also the pathological basis for acute disseminated LCH (Letterer–Siwe disease) and multifocal LCH (Hand–Schüller–Christian disease)—disorders which produce a spectrum of distinct clinical feature (see Chapter 22.3.9).

Epidemiology and aetiology

LCH affects about one in 560 000 adults, with an equal male to female ratio and a peak age of onset between 20 and 40 years. There is a strong association with smoking, with more than 90% of patients having smoked tobacco. Patients with pulmonary LCH have abnormal T-cell proliferative responses to tobacco glycoproteins and an increased secretion of bombesin-like peptides from neuroendocrine cells in the lung. Recently mutations in the mitogen-activated protein kinase pathway (such as the BRAF V600 mutation) have been identified in about half of tissue samples of LCH.

Clinical features

Cough and breathlessness are the most common symptoms, and about one-third of patients have systemic symptoms such as fever or weight loss. Pneumothorax occurs in about 25% of patients and may be recurrent and sometimes bilateral. About 25% of patients have no symptoms and the diagnosis is made incidentally from a chest radiograph.

In adult pulmonary LCH the clinical manifestations are usually confined to the lungs, but in 10–15% of cases lesions are also present in bone, skin, lymph nodes, and the posterior pituitary (sometimes causing diabetes insipidus).

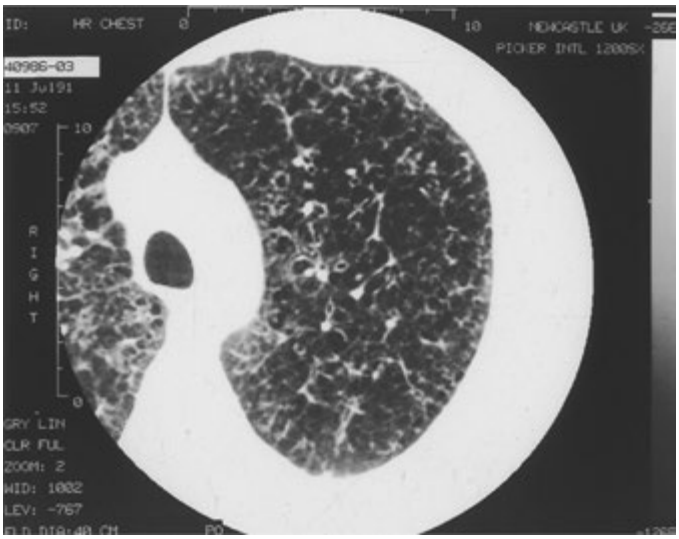

Fig. 18.14.5.1 High-resolution CT of a 45-year-old smoking man with biopsy-proven Langerhans' cell histiocytosis, showing centrilobular nodules, cysts, and reticulation.

Investigation and diagnosis

The chest radiograph typically shows nodules, reticulation, and cysts in the mid and upper zones symmetrically, with sparing of the costophrenic angles; the lung volumes are often normal or increased, in contrast with many other fibrotic lung diseases. High-resolution CT (Fig. 18.14.5.1) characteristically shows multiple centrilobular nodules with cavitation, progressing to cyst formation and fibrosis in later stage disease.

Pulmonary function tests often show a mixture of airways obstruction, air trapping with elevated residual volume, and impaired diffusing capacity for carbon monoxide.

Typical clinical and CT features may be sufficient for diagnosis, but video-assisted thoracoscopic lung biopsy is sometimes required. The characteristic histopathological features are mitotically active Langerhans' cells forming nodules and granulomas with a surrounding inflammatory cell infiltrate of lymphocytes, macrophages, and eosinophils (hence the previous diagnostic labels of eosinophilic granuloma and Langerhans' cell granulomatosis). Langerhans' cells are identified by immunostaining of the CD1a membrane antigens or the S100 intracellular protein, and by electron microscopy showing Birbeck granules—rods of tennis racket-shaped structures unfolding from the cell membrane. In advanced disease, fibrosis and honeycombing predominate. Biopsies often show features of other smoking-related diseases such as desquamative interstitial pneumonia, obstructive bronchiolitis, and emphysema. Langerhans' cells can also be identified in bronchoalveolar lavage fluid, but this is neither sensitive nor specific in diagnosing the disease.

Management

Because pulmonary LCH varies greatly in its clinical course, management has to be individualized for the particular patient. Smoking cessation is crucial. About 25% of cases resolve, 50% stabilize, and 25% progress with loss of lung function. Corticosteroid therapy is usually given for progressive disease, but the benefits are unclear. Cytotoxic drugs such as vinblastine, cyclophosphamide, and cladribine show benefit in some reported cases. Treatment with inhibitors of mutated BRAF has resulted in stabilization or improvement in some patients. Pleurodesis or pleurectomy may be needed for recurrent pneumothoraces and, in view of the risk of bilateral pneumothorax, is best considered sooner rather than later. Lung transplantation is the main option for patients with advanced disease, although recurrence in the transplanted lungs has been described.

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18.14.6 Lymphangioleiomyomatosis

S.J. Bourke

ESSENTIALS

Lymphangioleiomyomatosis is characterized by cystic destruction of the lungs due to abnormal proliferation of smooth muscle cells. It is caused by mutations of the genes encoding hamartin and tuberin, sometimes in association with tuberous sclerosis. CT imaging shows characteristic multiple thin-walled cysts. There is usually progressive airways obstruction and impaired gas diffusion, and two-thirds of patients suffer pneumothoraces. Sirolimus can stabilize lung function and improve symptoms. Lung transplantation is the main option for advanced disease.

Introduction

Lymphangioleiomyomatosis (LAM) is a rare disease in which lymphatics ('lymph'), blood vessels ('angio'), and airways are infiltrated by proliferating abnormal smooth muscle cells ('leiomyo'),

resulting in cystic destruction of the lungs, pneumothoraces, chylous effusions, and haemorrhage. LAM cells have low-grade neoplastic properties with enhanced proliferation and invasiveness. LAM can occur as a sporadic disorder or in association with tuberous sclerosis.

Pathogenesis

Both sporadic and tuberous sclerosis-associated LAM result from mutations of the tumour suppressor genes *TSC1* and *TSC2*, which encode hamartin and tuberin that form a cytoplasmic complex that inhibits the protein mTOR. Loss of suppressor function upregulates mTOR, resulting in proliferation of LAM cells.

Sporadic LAM occurs exclusively in women, predominantly between the menarche and the menopause. Exceptionally rare cases of LAM have been reported in men with tuberous sclerosis, but the disease is almost confined to women. The origin of LAM cells is unknown but they might arise from the uterus, and oestrogen and progesterone receptors have been found in some LAM cells.

Sporadic LAM is due to somatic (noninherited) mutations in the *TSC1* and *TSC2* genes and occurs in about 2 in a million women. Tuberous sclerosis results from a germ-line mutation of the *TSC1* and *TSC2* genes and is an autosomal dominant inherited disorder (OMIM 191 100) whose manifestations include epilepsy, learning difficulties, skin lesions (angiofibromas, shagreen patches), and hamartomas in the brain, kidneys, and other organs (see Chapter 24.17). Most women with tuberous sclerosis ultimately develop evidence of LAM on CT as they get older, with 63% developing symptoms and 12.5% dying of LAM.

Clinical features and diagnosis

Pneumothorax occurs in about two-thirds of patients with LAM and is a common mode of presentation. Other manifestations include breathlessness from progressive parenchymal involvement, cough, haemoptysis, and chest pain. Involvement of the thoracic duct may result in chylous pleural effusions and ascites. Other abdominal features include renal angiomyolipomas, cystic lymphatic masses, and lymphadenopathy. Renal angiomyolipomas are present in about 50% of patients: they rarely cause symptoms, but bleeding may require treatment by embolization or surgical resection.

The chest radiograph typically shows diffuse small cysts with reticular shadowing, but normal or increased lung volumes. Lung function tests usually show progressive airways obstruction and reduced gas transfer. The CT features are sufficiently characteristic to establish the diagnosis in many cases, with well-defined cystic airspaces with thin walls distributed throughout both lungs (Fig. 18.14.6.1), and more widespread use of CT imaging is detecting milder cases in an extended spectrum of patients including some postmenopausal women.

Lung biopsy may be needed where there is doubt about the diagnosis: this shows abnormal infiltration by smooth muscle cells, which can be identified by immunohistochemical staining for the HMB45 (human melanoma black) antigen. Aspirated pleural fluid may show diagnostic clusters of immature muscle cells. The serum levels of vascular endothelial growth factor, VEGF-D, are elevated, and this may be a useful biomarker of the disease.

Fig. 18.14.6.1 CT scan of a 37-year-old woman with pulmonary lymphangioleiomyomatosis and tuberous sclerosis. She had experienced sequential spontaneous pneumothoraces affecting each side. The scan shows multiple thin-walled cysts throughout the lung.

Management and prognosis

Sirolimus inhibits the protein mTOR and has been shown to stabilize lung function, reduce symptoms, and improve quality of life and functional performance, such that it is now the recommended treatment for patients with progressive disease. Treatment has to be continued indefinitely, with the risk of adverse effects, and there is some evidence that low-dose therapy may sufficient.

Patients should avoid exogenous oestrogens, including oestrogen contraceptives or hormonal replacement therapy. Pregnancy may be associated with an increased risk of pneumothorax and loss of lung function. Hormonal therapy with progesterone or tamoxifen appears to be ineffective; other antioestrogen therapies, such as letrozole, are being studied. Recent research shows that human LAM lungs express the immune checkpoint ligand PD-L1 and that treatment of a mouse LAM model with anti-PD-1 antibody improved survival.

Pneumothorax is common and likely to recur such that medical or surgical pleurodesis is advisable. Lung transplantation is the main option for patients with advanced LAM, but recurrence of the disease due to migration of LAM cells to the donor lung has been reported.

The clinical course of LAM is variable, but by 10 years after diagnosis, 55% of patients are breathless on daily activities, 20% require supplemental oxygen, and 10% have died.

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18.14.7 Pulmonary alveolar proteinosis

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ESSENTIALS

In 90% of cases pulmonary alveolar proteinosis is caused by autoimmune antibodies to GM-CSF which impair the function of alveolar macrophages in clearing surfactant from the alveoli, giving rise to impaired gas exchange, breathlessness, and respiratory failure. Chest radiography shows extensive alveolar shadowing simulating pulmonary oedema, and CT scanning shows a characteristic 'crazy paving' pattern. The presence of GM-CSF antibodies in the serum is useful in diagnosis. Bronchoalveolar lavage or lung biopsy demonstrates alveolar secretions that are strongly PAS-positive. Treatment is by physical removal of the lipoproteinaceous material from the alveoli by whole-lung lavage.

Massive inhalation of dust and fumes may overwhelm macrophage function, giving rise to secondary pulmonary alveolar proteinosis.

Introduction

Pulmonary alveolar proteinosis was first described by Rosen *et al.* in 1958. It is a rare disease, characterized by the accumulation of surfactant lipids and proteins in the alveoli, giving rise to impaired gas exchange, breathlessness, and respiratory failure. Detailed registry studies in Japan showed an incidence of 0.5 per million and a prevalence of 6.2 per million, with a median age of onset of 51 years and a male:female ratio of 2:1, but the disease seems to be less common in other countries. Whole-lung lavage is effective in removing the lipoproteinaceous material from the alveoli.

Aetiology and pathogenesis

Surfactant is secreted by type 2 pneumocytes in the alveolar wall. It is a lipoproteinaceous material consisting of the phospholipid dipalmitoyl phosphatidylcholine which has an important role in reducing the surface tension of the alveoli, maintaining patency and preventing collapse. In pulmonary alveolar proteinosis there is defective clearance of surfactant, and this may arise by different mechanisms such that the disease is classified into three distinct forms: autoimmune, secondary, and hereditary.

Autoimmune

Autoimmune pulmonary alveolar proteinosis is the commonest form of the disease, accounting for 90% of cases. It is due to the development of systemic neutralizing antibodies to granulocyte macrophage-colony stimulating factor (GM-CSF). The mechanisms giving rise to GM-CSF autoantibodies are unclear, and these patients do not usually have any other autoimmune diseases. The alveolar macrophage has an essential role in clearing surfactant, and in the presence of GM-CSF antibodies their function is impaired, clearance of surfactant is reduced, and the alveoli become filled with this lipoproteinaceous material. Inflammation and/or fibrosis are not usually found, and alveolar architecture is well preserved. Secondary infection can, however, give rise to additional problems.

Secondary

Secondary pulmonary alveolar proteinosis accounts for about 9% of cases and arises as a complication of other diseases. Acute inhalation of dust and fumes may cause the condition, presumably by overwhelming macrophage function, much as silica is known to impair macrophage handling of tubercle bacilli. This has been best described in acute silicosis (silicoproteinosis), which arises within months of massive exposure to respirable crystalline silica. It has also occurred after inhalation of aluminium, titanium, insecticides, or petrol fumes.

Secondary pulmonary alveolar proteinosis may also occur as a complication of haematological disorders such as myelodysplasia, leukaemia, or lymphoma, and may also occur in association with immunodeficiency states and chronic infections such as histoplasmosis, *Pneumocystis jirovecii*, and mycobacterial infections. The mechanisms underlying pulmonary alveolar proteinosis in these disorders are unclear, but are thought to involve a reduction in the number or function of alveolar macrophages. These patients do not have GM-CSF antibodies.

Hereditary

Hereditary pulmonary alveolar proteinosis is a very rare form of the disease caused by mutations of the genes involved in GM-CSF signalling, particularly mutations in the CSF2RA and CSF2RB genes encoding for the GM-CSF receptor α- and β-chains. It presents as progressive breathlessness in young children. These patients do not have GM-CSF autoantibodies, but have increased serum GM-CSF levels which can be a useful pointer in identifying the diagnosis.

Clinical features and diagnosis

The clinical features depend on the stage and context of the disease. Typically the patient presents with progressive shortness of breath. Cough is common but is usually nonproductive. Some patients are seen at a time when they have developed a superadded infection, when they may then present with acute symptoms of fever, cough, and breathlessness, but they may well have had more prolonged insidious symptoms. Some patients are found to have extensive shadowing on an incidental chest radiograph before they have noticed symptoms.

Physical examination is often normal despite extensive alveolar shadowing on the radiograph, but crackles may be present and some patients have clubbing. In advanced disease patients develop severe breathlessness, cyanosis, and respiratory failure.

Investigation

The predominant abnormality in pulmonary function tests is a restrictive ventilatory defect with a reduction in lung volumes and gas diffusion. As the disease progresses the patients become hypoxic, initially on exercise and then even at rest.

The chest radiograph typically shows an extensive bilateral alveolar filling pattern, which often initially suggests pulmonary oedema or pneumonia. CT scanning shows a very characteristic pattern of widespread air space consolidation with thickened interlobular septa, producing a so-called 'crazy paving' pattern (Fig. 18.14.7.1). Some other conditions can give a similar appearance, including lipoid pneumonia, diffuse lepidic adenocarcinoma (bronchoalveolar cell carcinoma) and pneumocystis pneumonia.

Bronchoalveolar lavage characteristically yields 'milky fluid' which consists of lipoproteinaceous material that stains a deep pink with periodic acid Schiff (PAS) stains. The material is negative on alcan blue stain, which differentiates it from mucins. There is a notable absence of inflammatory cells, but the macrophages are enlarged and contain abundant phospholipoprotein inclusions giving the appearance of 'foamy macrophages'.

Fig. 18.14.7.1 Computed tomography of a patient with pulmonary alveolar proteinosis, showing diffuse alveolar filling with septal thickening from oedema, giving a 'crazy pavement' pattern.

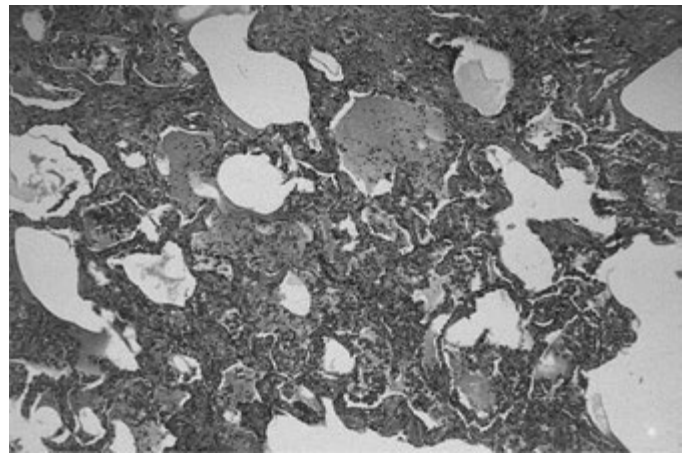

Fig. 18.14.7.2 Pulmonary alveolar proteinosis arising acutely following massive exposure to silica. Some alveoli are filled with a noninflammatory proteinaceous exudate, characteristic of pulmonary alveolar proteinosis. The lung interstitium shows fibrosis and inflammation, which can be attributed to acute silicosis (haematoxylin and eosin, medium magnification).
Courtesy of Dr D. E. Banks.

Lung biopsy is not often necessary, but pathological findings confirm a similar appearance to bronchoalveolar lavage fluid (Fig. 18.14.7.2). The alveolar architecture is usually well preserved, although there is septal thickening from oedema. Electron microscopy shows lamellar bodies within the alveolar lumen representing phospholipids.

In autoimmune pulmonary alveolar proteinosis the demonstration of serum GM-CSF autoantibodies is both sensitive and specific in the diagnosis. These are not found in patients with secondary causes of pulmonary alveolar proteinosis, and it is important to obtain a detailed occupational and environmental history to assess for any inhalation of dust or fumes, and to identify any associated haematological conditions. In the very rare form of hereditary pulmonary alveolar proteinosis in children, GM-CSF antibodies are also absent, but these children often have high serum GM-CSF levels which may be a useful pointer to the diagnosis.

Bronchoalveolar lavage is also useful in identifying any infections which may complicate pulmonary alveolar proteinosis. Because of impaired macrophage function these patients are vulnerable to opportunistic infections with nocardia, cryptococcus, cytomegalovirus, histoplasmosis, and mycobacteria.

Management and prognosis

Whole-lung lavage

The standard treatment of pulmonary alveolar proteinosis is whole-lung lavage, which is effective in physically removing the lipoproteinaceous material from the alveoli, thereby restoring gas

exchange, improving macrophage function and reducing the occurrence of secondary infections. This is a complex procedure, best performed in specialist centres with experience in the technique. Under general anaesthesia patients are intubated with a double-lumen endotracheal tube. The appropriate placement of the tube with isolation of each lung is crucial. Ventilation is then given to one lung while the other lung is lavaged with warmed normal (0.9%) saline, in aliquots of 250–500 ml, with total volumes of up to 60 litres. Effective removal of the lipoproteinaceous material may be enhanced by positional changes, assisted clearance and percussion physiotherapy during the procedure. The fluid removed is initially milky but clears as the procedure progresses. The procedure is then reversed so that the other lung is treated.

Most patients show substantial clinical improvement after whole-lung lavage, with immediate improvement in oxygenation. Lung function tests show that the vital capacity improves within one week and continues to improve over the subsequent year. The transfer factor for carbon monoxide tends to improve more slowly, with no increase at one week but substantial improvement over the next six months. The longer-term outcome after whole-lung lavage is variable: about 50% of patients go into prolonged remission after one lavage, but some need repeat lavage as the lipoproteinaceous material reaccumulates.

GM-CSF

Autoimmune pulmonary alveolar proteinosis may also be treated by GM-CSF, which can be administered subcutaneously or by aerosol. A meta-analysis of GM-CSF treatment showed a response rate of about 60%, varying between 40 and 90% in different studies, with a relapse rate of about 30%. GM-CSF therapy is associated with minor systemic complications such as fever, and local complications at the site of injection. The optimal indication, dose and duration of therapy, and the sfactors predicting response and relapse, all need further clarification, but this treatment may be particularly useful in those with a poor response to whole-lung lavage or in those requiring repeated lavages.

Other treatments

Plasmapheresis has been used to reduce levels of GM-CSF autoantibodies, but this did not result in clinical improvement in the severity of the lung disease. Rituximab, a monoclonal antibody directed against the B-lymphocyte antigen CD20, has also been used, and resulted in a reduction in GM-CSF antibody levels and improvement in some patients, but whole-lung lavage remains the standard treatment.

Recurrence of alveolar proteinosis has been reported in a patient who underwent lung transplantation for this condition. Secondary infections can occur and need to be promptly identified and treated. The occurrence of infection is reduced by effective whole-lung lavage, which restores macrophage function.

Prognosis

Seymour and Presneill reviewed 343 published cases and found survival rates of 79% (2 years), 75% (5 years), and 68% (10 years). Of the 69 deaths, 60 were attributed to pulmonary alveolar proteinosis—47 (72%) from respiratory failure, 12 (18%) from complicating infection, and one (2%) from cardiac arrest during lavage. The actuarial 5-year disease-specific survival was 88%. Of those dying within 5 years, more than 80% did so during the first year after diagnosis: thereafter there was a significantly reduced risk of mortality.

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18.14.8 Pulmonary amyloidosis

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ESSENTIALS

Pulmonary amyloidosis is characterized by the deposition of monoclonal immunoglobulin light chain amyloid protein locally or diffusely in lung tissue. Local amyloid deposits in the airways, produced by B-cell clones within local tissues, may cause stridor, wheeze, cough, and haemoptysis. Diffuse alveolar deposition can occur as a complication of systemic amyloidosis when the AL protein is derived from immunoglobulins produced from bone marrow B cells in diseases such as multiple myeloma, lymphoma, and monoclonal gammopathy.

Introduction

Amyloidosis is a diverse disease characterized by the deposition of amyloid proteins in extracellular tissues (see Chapter 12.12.3). The aetiology and manifestations vary depending on the different precursor amyloid protein and whether deposition is local or systemic.

Several different amyloid proteins have been described, but the two main types relevant to lung disease are reactive systemic (AA) amyloidosis, in which the amyloid protein is derived from the acute phase protein serum amyloid A, and monoclonal immunoglobulin light chain (AL) amyloidosis, in which the amyloid protein is derived from monoclonal immunoglobulin light chains. In amyloidosis these proteins are deposited in extracellular tissue in an abnormal fibrillar form as aggregates of misfolded protein with an abnormal β-sheet conformation that is insoluble and resistant to proteolysis.

Amyloid deposits are demonstrated in biopsies of affected tissues by Congo red dye producing green birefringence when viewed in polarized light. The protein type can be identified by immunostaining or proteomic analysis. Amyloid deposits also contain some normal nonfibrillar plasma glycoprotein, serum amyloid P (SAP), and radiolabelled SAP scintigraphic imaging is available in some specialist centres and is useful in defining the extent and burden of disease in patients.

AA systemic amyloidosis

This form of amyloidosis does not cause pulmonary disease although amyloid may be present in the pulmonary vessels at postmortem examination. In a large series of 374 patients with systemic AA amyloidosis, Lachmann *et al.* found that bronchiectasis was the underlying cause in 5%, and tuberculosis in 1% of patients, but in no case did AA amyloidosis cause clinically significant lung disease. Treatment is aimed at controlling the underlying inflammatory disease to reduce the overproduction of serum amyloid proteins.

AL amyloidosis

In systemic AL amyloidosis the lungs show evidence of amyloid deposition in about 50% of patients, but only rarely does this give rise to symptoms. However, diffuse alveolar–interstitial deposition causes progressive impairment of gas diffusion in some cases.

In local AL amyloidosis, isolated nodules of amyloid are deposited in the larynx, trachea, bronchial tree, or lung parenchyma. These nodules arise from B-cell clonal expansion in the tissues close to the amyloid deposits, such that the disease is localized without systemic involvement. The factors provoking local B-cell clonal expansion and local amyloid nodules are not understood.

Clinical features

The clinical features of pulmonary amyloidosis are diverse and depend on the location and pattern of amyloid deposits.

Localized laryngotracheobronchial disease

Amyloid deposits may produce nodules or more extensive plaques in the walls of the airways or the peribronchial tissues. In laryngeal amyloidosis the key features are hoarseness, stridor, and cough. In the bronchial tree symptoms depend on the anatomical location, but amyloid deposits may cause cough, obstruction, and haemoptysis. Obstruction of airways may lead to atelectasis of a lobe or segment with distal infection. Central lesions may pose particular difficulty for intubation and the administration of anaesthesia. When a single lesion is involved it may simulate the effects of a bronchial adenoma, appearing as a polypoid mass on endoscopic inspection. CT scans and bronchoscopy give anatomical definition of the disease, but biopsy is necessary to demonstrate amyloid.

Localized parenchymal nodules

Discrete nodules or masses, which may be single or multiple, are seen within the lung parenchyma on the chest radiograph and CT. They rarely cause symptoms or disrupt lung function and may eventually calcify, cavitate, or even ossify. They are likely to simulate bronchial neoplasms if single and hence biopsy and surgical resection are often performed. Caution in conducting a biopsy on lesions is required because amyloid deposits may disrupt blood vessels, preventing vasoconstriction and contributing to an increased risk of bleeding.

Diffuse alveolar–interstitial disease

Amyloid deposited diffusely throughout the alveolar walls and interstitium of the lung is a rare manifestation of AL amyloidosis (Figs. 18.14.8.1 and 18.14.8.2). Here the lung disease is part of more widespread systemic amyloidosis and these patients often also have cardiac and renal amyloidosis. There have been a few reports of AA amyloid affecting the lungs, but the fibril type may have been misidentified and all studies in which the fibril protein has been sequenced show AL type amyloid.

Systemic symptoms of tiredness, malaise, and weight loss are common. There is progressive breathlessness and a dry cough, with prominent crackles on examination. Lung function testing shows impairment of gas diffusion and restriction of lung volumes. The prognosis is poor, with progressive hypoxia and respiratory failure, although death more commonly results from cardiac or renal involvement.

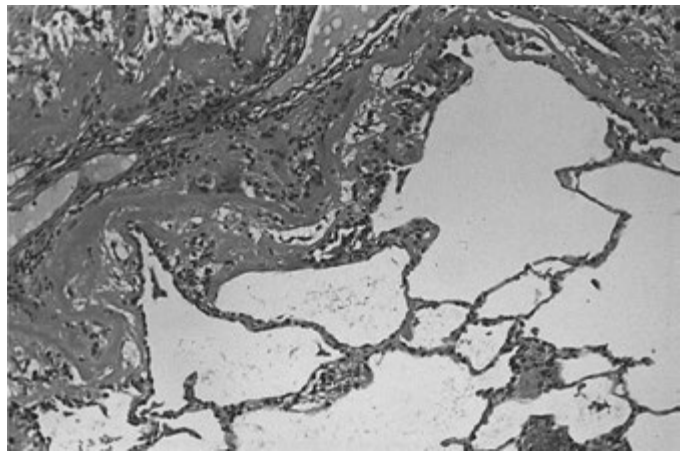

Fig. 18.14.8.1 Alveolar–interstitial-type amyloidosis of the lung. Staining with haematoxylin and eosin (medium magnification) reveals interstitial deposits of hyaline eosinophilic material with a foreign body type giant cell response in adjacent tissue. This is an almost unique feature of amyloidosis affecting the lung.
By courtesy of Dr T. Ashcroft.

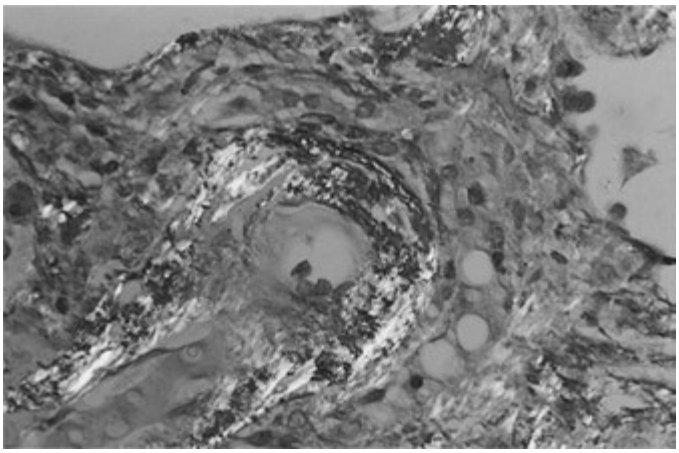

Fig. 18.14.8.2 Alveolar–interstitial type amyloidosis of the lung. Staining with Congo red stain under polarized light (high magnification) demonstrates the characteristic dichroic birefringence.
By courtesy of Dr T. Ashcroft.

Other manifestations

Exudative pleural effusions can occur from amyloid deposits directly involving the pleura. Transudative pleural effusions and pulmonary oedema are often complications of amyloid cardiomyopathy or nephrotic syndrome. Respiratory muscle weakness has been reported due to infiltration of the diaphragm and skeletal muscles by amyloid. Lymph node enlargement may be seen on CT images. Macroglossia may cause or aggravate obstructive sleep apnoea. The pulmonary vasculature often contains deposits of amyloid at post-mortem examination. This is usually of no clinical consequence but has been reported to cause pulmonary hypertension and may be associated with an increased risk of bleeding when amyloid tissue is biopsied.

Management and prognosis

Local deposits of amyloid in the larynx, trachea, or bronchi may require treatment by endoscopic interventions, with mechanical debulking by forceps resection or laser therapy. This is effective in relieving airway obstruction, but there is a risk of provoking bleeding and recurrence is common. Stenting may also be used to maintain airway patency. Radiotherapy has also been deployed successfully, and in certain circumstances may be a better option with less risk of bleeding or recurrence.

Amyloid deposits in the lung parenchyma often do not give rise to symptoms and may not require treatment, but they simulate bronchial carcinoma and may therefore be resected. Systemic AL amyloidosis may be treated by chemotherapy, using agents such as melphalan to reduce the production of immunoglobulin light chains.

Diffuse alveolar amyloidosis has a poor prognosis, particularly because it is associated with cardiac and renal amyloidosis. Lung transplantation has very rarely been performed for pulmonary amyloidosis.

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18.14.9 Lipoid (lipid) pneumonia

S.J. Bourke

ESSENTIALS

Exogenous lipoid pneumonia occurs when animal, vegetable, or mineral oils are aspirated or inhaled into the lungs, provoking a foreign body reaction with chronic inflammation. Typical symptoms are cough and breathlessness. The chest radiograph and CT may show interstitial thickening, with areas of consolidation that may coalesce into a mass (paraffinoma) which simulates carcinoma. Bronchoalveolar lavage and biopsy show lipid-laden macrophages.

In endogenous lipoid pneumonia the lipids are derived from surfactant and cholesterol released from decaying cells distal to bronchial obstruction.

Introduction

Lipoid pneumonia is an unusual form of lung disease resulting from the accumulation of lipids in the alveoli, where they provoke a foreign body reaction with associated inflammation and sometimes local fibrosis. The lipids may be endogenous or exogenous in origin, and the clinical mechanisms and circumstances differ accordingly.

Endogenous lipoid pneumonia is usually part of another lung disease, notably bronchial obstruction from carcinoma or bronchiolitis, where cholesterol and lipid–rich surfactant accumulate in the alveolar macrophages.

Exogenous lipoid pneumonia is caused by the aspiration or inhalation of animal, vegetable, or mineral oil, or hydrocarbons such as petroleum-based substances (**Box 18.14.9.1**). When exogenous mineral or vegetable lipids are deposited in the lung, they

Box 18.14.9.1 Lipoid pneumonia

Exogenous lipoid pneumonia

Aspiration

- Liquid paraffin laxatives
- Paraffin-based nasal jelly
- Cod liver oil
- Milk feeds
- Ghee feeds
- Nasogastric feeding
- Cosmetic oils
- Petrol-siphoner's lung

Inhalation

- Metal working fluid
- Oil mists
- Blackfat tobacco smoking
- Fire fighters
- Fire eater's lung

Endogenous lipoid pneumonia

- Bronchial obstruction
- Bronchiolitis
- Niemann–Pick disease
- Fat embolism

are usually relatively inert but difficult to remove. Lung lipases have little effect, and macrophages are slow to transport the free or emulsified material into the lymphatics, such that they are retained in the lung for a long time. The result is often a chronic low-grade inflammatory response that may lead to local fibrosis. Animal lipids are more readily degraded by lung lipases, releasing irritating fatty acids and causing a brisk and more widespread pneumonitis, particularly if lipid material is inhaled in large quantities.

Exogenous lipoid pneumonia

Aetiology

Acute lipoid pneumonia

Acute lipoid pneumonia is the result of an episode of massive exposure to petroleum-based products. This usually occurs as a result of an accident or specific circumstances, such as 'fire eater's lung' or 'petrol-siphoner's lung'. In fire eating the performer blows out a mouthful of a flammable petroleum-based liquid against a burning stick, creating an aerosol that burns around the stick. In siphoning petrol, fluid may be sucked into the mouth and aspirated during ingestion or when vomiting. Shipwrecked sailors have suffered lipoid pneumonia from aspirating floating oil in the sea. A high level of lipid deposition in the lung can produce severe acute respiratory failure, as well as systemic effects involving other organs.

Chronic exogenous lipoid pneumonia

Chronic exogenous lipoid pneumonia is an indolent disease resulting from repeated aspiration or inhalation of lipids into the lung. Diagnosis is based upon identifying a history of exposure to exogenous lipid, and this has been described in a diverse range of settings and circumstances. In infants and children exogenous lipoid pneumonia has occurred as the result of feeding debilitated malnourished children with milk, ghee (clarified butter), or liquids with a high lipid content. Administration of cod liver oil to reluctant children has also resulted in deposition of lipid in the lungs. Sometimes repeated use of petroleum-based nasal jelly is the source of the exogenous lipid. In parts of India there was a common practice of cleaning the mouth, throat, and nose of infants with oil, and this resulted in a high incidence of lipoid pneumonia. In older people lipoid pneumonia has most often occurred from the regular use of liquid paraffin as a laxative, taken each night for chronic constipation. Nasogastric feeding can also result in repeated deposition of lipid in the lungs. Often there are associated problems which predispose to aspiration, such as an impaired cough reflex, gastro-oesophageal reflux, or neurological disease, causing difficulties in swallowing or impaired consciousness.

In the occupational setting lipid inhalation may occur in firefighters exposed to oil mists and burning fats, and in factory workers inhaling metal working fluid contaminated with lubricant oils. Local customs and habits may cause lipid pneumonia in particular circumstances, such as the blackfat tobacco smokers of Guyana. Blackfat is a tobacco leaf to which mineral oil and Vaseline are added for flavouring, leading to recurrent inhalation of lipids.

Clinical features

The clinical features depend on the irritant properties of the lipid material and the dose retained in the lung, and whether any additional materials have been aspirated into the lungs.

Chronic low-grade aspiration of lipid often produces no immediate symptoms and the affected subject may present by chance with an abnormal chest radiograph. However, in about 50% of cases there is a chronic pneumonic illness with productive cough, low-grade fever, and occasionally haemoptysis. Repeated aspiration may lead to fibrotic shrinkage of the affected segments, usually in the lower lobes or the middle lobe. Sometimes the radiographic appearances may closely simulate bronchial carcinoma and surgical resection may be undertaken, revealing a characteristic granulomatous mass (paraffinoma).

When more substantial quantities are aspirated the radiographic abnormalities are more diffuse, and when the lipid material is more reactive an acute pneumonic illness occurs. CT may allow the identification of lipid material by its low density (similar to body fat, –150 to –80 Hounsfield units, compared with + 50 to + 150 units for solid tumours) and also show patchy areas of ground-glass attenuation and interstitial thickening, thereby producing a 'crazy paving' pattern.

Diagnosis is crucially based on identifying exposure to exogenous lipid, and this often requires a detailed history, concentrating on particular risk factors. Identifying lipid material and lipid-laden macrophages in bronchoalveolar lavage fluid or sputum is helpful, but this must be interpreted in the context of the full clinical circumstances and the presence of any diseases associated with endogenous lipoid pneumonia. Transbronchial biopsy or surgical lung biopsy may be needed, and typically shows lipid-laden macrophages, multinucleated giant cells, and interstitial fibrosis (Fig. 18.14.9.1).

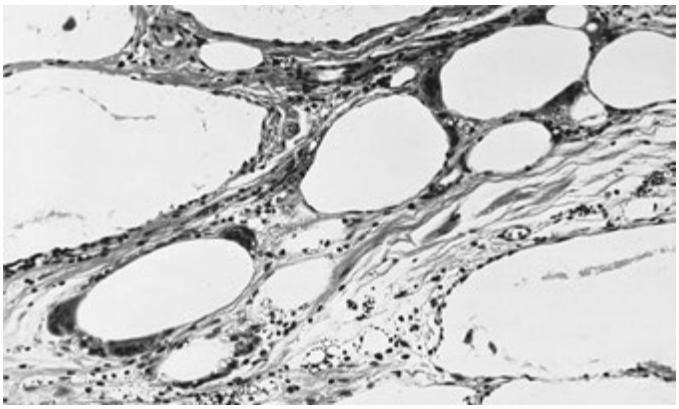

Fig. 18.14.9.1 Section of lung showing exogenous lipoid pneumonia due to aspirated paraffin. There is interstitial fibrosis containing oil vacuoles which are enclosed within multinucleated giant cells (haematoxylin and eosin stain, medium magnification).
By courtesy of Dr T. Ashcroft.

Prevention and management

Prevention of lipoid pneumonia is focused on minimizing any tendency to aspiration associated with impaired swallowing, and in persuading the user of vegetable and mineral oils to adopt alternative habits. Stopping further exposure to exogenous lipids is also important in the treatment of the disease. Corticosteroids have been used where there is associated inflammation, but their effectiveness is doubtful. In acute massive lipoid pneumonia treatment is largely supportive. Therapeutic bronchoalveolar lavage has occasionally been used in an attempt to remove lipid from the alveoli.

Endogenous lipoid pneumonia

Lipoid pneumonia is a feature of obstructive pneumonitis, particularly where there is occlusion of a bronchus by a carcinoma, but also in diseases characterized by bronchiolitis or chronic interstitial inflammation. In this situation the lipid is endogenous, consisting of cholesterol released from decaying cells and surfactant, which are taken up by macrophages. Macroscopically the area of lung shows consolidation with a characteristic yellow discolouration as a 'cholesterol pneumonia' or 'golden pneumonia'. Histologically there is an abundance of lipid-laden macrophages with cholesterol crystals on polarized light microscopy.

Excess lipid in the lungs is also a feature of Niemann–Pick lipid-storage disease and fat embolism to the lungs from fractured bones. Therefore, although lipid-laden macrophages in bronchoalveolar lavage fluid are a characteristic feature of exogenous lipoid pneumonia, endogenous causes also need to be considered.

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18.14.10 Pulmonary alveolar microlithiasis

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ESSENTIALS

Pulmonary alveolar microlithiasis is characterized by the deposition of calcium phosphate in the alveolar air spaces as a result of mutations of the *SLC34A2* gene. The patient is often symptom-free when the diagnosis is made after a chest radiograph is taken incidentally and reveals calcified micronodules, but typically the disease progresses to respiratory failure over about 10–20 years. Etidronate has led to improvement in some cases that have been detected early. Lung transplantation is the main option in advanced disease.

Introduction

Pulmonary alveolar microlithiasis is a rare lung disease in which calcium phosphate is deposited within the alveolar spaces forming microliths, as a result of mutations of the *SLC34A2* gene. The diffuse microliths give a characteristic appearance of calcified micronodules on a chest radiograph, sometimes described as 'sandstorm lung'. About 1200 patients with pulmonary alveolar microlithiasis have been reported in the medical literature since its initial description in 1918. The disease occurs worldwide, but predominantly in Turkey, Japan, India, America, and the Middle East, and about 25% of reported cases have been of Turkish descent.

Pathogenesis

The disease is an autosomal recessive condition caused by mutations of the solute carrier family 34, member 2 gene, *SLC34A2*, on the short arm of chromosome 4. Several different mutations have been described, including frameshifts, chain terminations, and amino acid substitutions. The gene has 13 exons and encodes a 690-amino acid protein, the sodium-phosphate cotransporter, which is primarily expressed in the apical membrane of alveolar type II cells. The recycling of surfactant releases phosphate into the alveoli, and *SLC34A2* gene mutations result in impaired clearance of phosphate by the sodium-phosphate transporter. The accumulated phosphate binds calcium, forming calcium-phosphate microliths, which are typically about 1 mm in diameter. Initially they are predominantly located in the lower lobes, but progress to involve all areas of the lungs and extend to fill the entire alveolar space, leading to damage to the alveolar membrane and fibrosis, with impairment of gas exchange.

The diffuse micronodular calcification of pulmonary alveolar microlithiasis is very different from dystrophic or metastatic lung calcification seen in other circumstances. Dystrophic lung calcification consists of calcium deposition in tissue damaged by infections such as tuberculosis, histoplasmosis, or varicella pneumonia, or diseases such as chronic sarcoidosis, silicosis, or longstanding mitral stenosis. Metastatic lung calcification refers to the phenomenon where there is calcium deposition in the interstitium of normal lungs as a result of hypercalcaemia, primary or secondary hyperparathyroidism, vitamin D intoxication, diffuse myelomatosis, or chronic renal failure. In pulmonary alveolar microlithiasis there is no abnormality of calcium metabolism and serum calcium and phosphate levels are normal.

In most cases of pulmonary alveolar microlithiasis the lungs are the only organs affected, but the gene is expressed to a lesser extent in other tissues, and calcium deposits have been occasionally found in the kidneys, seminal vesicles, urethra, gallbladder, heart valves, and arteries.

Clinical features and diagnosis

The diagnosis is often made before symptoms have developed when a chest radiograph is performed for other reasons, and shows a dramatic typical 'sandstorm' pattern of diffuse bilateral calcified micronodules (Fig. 18.14.10.1). The dramatic radiographic appearances are typically out of proportion to the absence of symptoms or signs at this stage. However, the disease gradually progresses over several decades, with symptoms typically arising at about the age of 30–40 years. Breathlessness and a dry cough are the dominant symptoms. Haemoptysis and chest pain occur occasionally. As the disease progresses lung function tests show a restriction of lung volumes with impaired gas diffusion. In advanced stage disease respiratory failure develops with hypoxaemia and hypercapnia, pulmonary hypertension, and right ventricular failure. Crackles, clubbing, and signs of respiratory failure are late features. In some cases, subpleural cysts give rise to recurrent pneumothoraces, and pleural adhesions may become prominent.

Fig. 18.14.10.1 A chest radiograph showing the typical 'sandstorm' appearances of pulmonary alveolar microlithiasis with micronodular calcific densities throughout the lungs.
http://www.ispub.com/ostia/index.php?xmlFilePath=journals/ijpm/vol9n1/pam.xml

The diagnosis can usually be made from the characteristic radiographic appearances of profuse, small, calcified nodules (Fig. 18.14.10.1). Initially the calcified micronodules are predominantly situated in the mid and lower zones, but gradually these progress to all areas. The pattern is different from other causes of calcification such as chronic sarcoidosis, healed calcified varicella pneumonia, pneumoconiosis, histoplasmosis, and miliary tuberculosis, or chronic renal failure.

Computed tomography demonstrates the numerous sand-like calcifications and sometimes also shows subpleural cysts and fibrosis. Lung biopsy is rarely necessary for diagnosis, but typically shows numerous intra-alveolar rounded calcified microliths. DNA sequencing of the *SLC34A2* gene can be undertaken, and other family members can be tested for the disease.

Serum levels of calcium and phosphate are usually normal, but elevated serum concentrations of surfactant protein SP-A and SP-D

have been noted, and might be useful in monitoring the activity and progression of the disease.

Treatment

Etidronate, a bisphosphonate, reduces the formation of calcium hydroxyapatite crystals and has led to clinical and radiological improvement in some cases, particularly in childhood, but seems to be ineffective in adults with advanced disease.

Lung transplantation is the main treatment option to be considered in advanced stage disease and has improved the prognosis and quality of life for the small number of patients with pulmonary alveolar microlithiasis who have undergone this procedure. Transplant surgery can be difficult if there are severe adhesions between the lungs and the chest wall. Deaths post lung transplantation have been due to complications of transplantation such as obliterative bronchiolitis, and there has been no evidence of recurrence of alveolar microlithiasis up to 15 years post-transplantation.

Prognosis

The severity of the disease and prognosis are variable, and this may be influenced by the specific type of gene mutation. Survival of 10–20 years from the onset of symptoms is typical. At death, extensive areas of the chest radiograph show a dense 'whiteout' appearance due to the considerable accumulation of calcium. At post-mortem examination, the lungs are difficult to cut and are heavy and sink in water.

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18.14.11 Toxic gases and aerosols

Chris Stenton

ESSENTIALS

Acute exposure to noxious agents causes pulmonary effects that are determined by the size of aerosol particles and by the solubility of gases. Large particles (>10 um) and soluble agents such as CS gas, ammonia, or sulphur dioxide affect primarily the upper respiratory tract, causing lacrimation, blepharospasm, rhinitis, cough, and breathlessness. Nitrogen oxides, ozone, and other agents of low solubility affect mainly the lungs, with pneumonitis and pulmonary oedema that can develop 24 hours or more after exposure. Smoke inhalation, intermediate solubility gases such as chlorine, and overwhelming exposures have effects throughout the respiratory tract. Some inhaled gases such as carbon monoxide and methane act as simple asphyxiants. Other reactions occur, such as metal fume fever with zinc and cadmium, and pulmonary haemorrhage with crack cocaine.

Management is essentially supportive. Carboxyhaemoglobin and lactate levels should be measured with smoke inhalation. Consideration should be given to the possibility of delayed pulmonary oedema even if the patient is well initially.

Chronic effects such as asthma, pulmonary fibrosis, and bronchiectasis can follow acute inhalation injuries. These can occur without any obvious acute injury, and may be difficult to detect as the radiological and lung function abnormalities are subtle.

Introduction

The inhalation of toxic chemicals following accidents or through routine use is one of the commonest forms of workplace injury. There has been a resurgence of military and paramilitary exposure to toxic substances such as sulphur mustard in recent decades. Long term effects of these and other exposures is increasingly recognized, with disease of the small airways (constrictive bronchiolitis) the commonest outcome. Smoke inhalation from domestic fires involves exposure to numerous toxic agents and remains common.

Acute toxic injury to the respiratory tract

The acute effects of inhaled gases are determined largely by their solubility in water (Table 18.14.11.1). Soluble gases such as ammonia or sulphur dioxide dissolve in the secretions lining the upper respiratory tract and cause acute irritant effects there. The symptoms usually force the affected individual to withdraw from exposure and that limits adverse effects. Poorly soluble gases such as nitrogen oxides and ozone have little or no effect in the upper airways but penetrate to the alveoli and cause pneumonitis and pulmonary oedema, which often becomes apparent only several hours after exposure.

The effect of aerosols (airborne suspensions of substances that are normally solid or fluid) is largely determined by their particle size. Particles of more than 10 μm diameter are deposited chiefly in

Table 18.14.11.1 The effects of gases and vapours on the airways and lungs

Highly soluble gases and vapours with upper airway effects
Hydrogen chloride
Ammonia
Formaldehyde
Acrolein
Sulphur dioxide
Intermediate solubility gases causing upper airway effects and pneumonitis
Chlorine
Hydrogen sulphide
Low solubility gases causing pneumonitis
Nitrogen oxides
Ozone
Phosgene

the nose and oropharynx. Smaller particles penetrate to the alveoli. Gases of intermediate solubility such as chlorine, massive exposures, or mixed exposures (e.g. with smoke inhalation), are likely to have effects at all levels of the respiratory tract.

Clinical features

Acute airway effects

Soluble irritant gases

Aerosols of the riot control and antipersonnel agents CS 'gas' (2-chlorobenzylidene malononitrile), mace (CN; 2-chloroacetophenone), and pepper (capsaicin) are employed because of their acute irritant effects on the eyes and upper respiratory tract. Exposures to soluble irritant gases and other large particle aerosols cause similar symptoms.

A burning sensation develops in the eyes, nose, throat, and large airways within seconds, usually with lacrimation, blepharospasm, rhinitis, cough, and breathlessness. Symptoms generally settle within 30 minutes, although some effects may persist for up to 24 hours. With more marked exposure there may be laryngeal oedema and upper airway obstruction with progressive coughing, wheezing, and stridor. Full recovery remains the rule, but acute bronchospasm can be fatal and tracheobronchitis can lead to secondary infection. If consciousness is lost then there is likely to be greater penetration to the alveoli, and pulmonary oedema may develop. Some individuals are left with asthma that persists for months, or even indefinitely. The latter is known as acute irritant asthma or the reactive airways dysfunction syndrome.

Sulphur mustard

Sulphur mustard ($C_4H_8Cl_2S$) caused injury to many Iranians during the 1980–1988 Iran–Iraq war. It affects mainly the skin, eyes, nose, and upper respiratory tract. Symptoms progress over several hours to days with lacrimation, rhinorrhoea, and coughing. Airway oedema and inflammation can lead to the development of pseudomembranes that can slough and cause airflow obstruction. Pulmonary oedema, and secondary infection is common. Pulmonary problems are the principal cause of mortality within the first few weeks of exposure.

Burns

Between 20% and 30% of burn victims suffer from pulmonary complications. Improvements in the treatment of shock and sepsis have rendered inhalation injury the main cause of mortality. Thermal injury affects the upper airways causing oedema and narrowing. Soot particulates and toxic gases including ammonia, sulphur dioxide, chlorine, phosgene, nitrogen dioxide, aldehydes affect all levels of the respiratory tract. Carbon monoxide and hydrogen cyanide act as chemical asphyxiants. If fat or oil is involved, a lipoid pneumonia may ensue, particularly if combustion (or explosion) leads to oil nebulization (see Chapter 18.14.9).

Acute pneumonitis/ pulmonary oedema

Gases of low solubility such as oxides of nitrogen, ozone, or phosgene have little if any effect in the upper airways. They penetrate readily to the gas-exchanging tissues, where they cause pneumonitis and pulmonary oedema. The effects are exemplified by nitrogen dioxide generated by stored grain. Farm workers can develop silo-filler's lung when they enter or decap a contaminated silo. Typically breathlessness caused by pulmonary oedema develops several hours after exposure though presentation may be delayed for 24 hours or more. Nitrogen dioxide can also be generated by thermal oxidation of nitrogen in air when welding is carried out in poorly ventilated areas, and from the combustion of nitrogen-containing substances such as nitrocellulose.

A wide range of other chemical agents can cause acute pneumonitis. Household waterproofing and dirt repellent sprays often contain fluorocarbon polymers. When used in confined spaces they can cause acute chemical pneumonitis (Fig. 18.14.11.1) that on occasions has been fatal. Exposure to cadmium fumes from welding metal alloys can also cause acute and potentially fatal chemical pneumonitis. Mercury vapour and less commonly antimony, manganese, beryllium, vanadium, cobalt, tributyl tin, and halide salts have all been reported to cause similar problems. Acid anhydrides

Fig. 18.14.11.1 Acute lung injury following the use of a waterproofing spray in an enclosed area. Lung biopsy showed a desquamative interstitial pneumonia pattern.

From Nakazawa A, *et al*. (2014). Surgically proven desquamative interstitial pneumonia induced by waterproofing spray. *Intern Med*, 53, 2107–10.

used as cross-linking agents in the production of epoxy resins cause pneumonitis with prominent alveolar haemorrhage and haemolytic anaemia. Smoking crack cocaine can also cause diffuse alveolar damage with alveolar haemorrhage that presents up to 48 hours after exposure.

Nonpulmonary effects

Asphyxiants

Gases other than oxygen can act as asphyxiants by displacing oxygen from inhaled air. The most commonly encountered are CO_2 and methane produced by decomposing vegetable material. The accumulation of oxygen-deficient air from soil in wells during periods of low barometric pressure has led to asphyxiation of those climbing into them. Blackdamp in coal mines arises from the slow combustion of coal. Occasionally deoxygenated air can escape from disused mines and enter cellars of overlying houses posing a risk to unsuspecting residents.

Chemical asphyxiants such as carbon monoxide and hydrogen cyanide act by blocking oxygen uptake by haemoglobin or by inhibiting intracellular oxygen utilization. They are important considerations in the case of smoke inhalation as they may be associated with tissue hypoxaemia despite apparently normal arterial oxygen saturation and pO_2 measurements. On rare occasions they may require specific treatment such as hyperbaric oxygen for carbon monoxide intoxication or dicobalt edetate for cyanide poisoning.

Metal and polymer fume fevers

Metal fume fever and polymer fume fever are acute self-limiting conditions characterized by influenza-like symptoms with fever, myalgia, headache, malaise, cough, and mild breathlessness, beginning within 6 hours of exposure and resolving fully within 24 hours. They are distinguished from inhalation injuries by the greater prominence of systemic features and by the absence of chest radiograph abnormalities or hypoxaemia.

Metal fume fever is most commonly caused by exposure to zinc from welding galvanized (i.e. zinc-coated) steel, but can also be caused by copper, magnesium, and other metal fumes. Polymer fume fever is caused by exposure to heated fluoropolymers. Overheated frying pans, and fluoropolymer particles from sealant tape transferred from plumbers' hands onto cigarettes are recognized causes. Tachyphylaxis leads to progressively milder responses with repeated exposures, similar to the 'Monday fever' described in cotton workers.

Assessment and management

Supportive care

The initial treatment of acute inhalation injuries is essentially supportive. The affected individual should be moved to a safe area and potentially contaminated clothing removed to avoid secondary exposure. Carers should wear appropriate protective clothing to ensure that they themselves do not become contaminated.

Oxygen saturation should be monitored and oxygen administered if the patient is hypoxaemic or if there has been possible exposure to carbon monoxide or cyanide (e.g. from fires). Carboxyhaemoglobin, methaemoglobin, and lactate levels should be measured following smoke inhalation. Nebulized bronchodilators should be administered if there is bronchospasm, and oral corticosteroids considered. Early intubation may be necessary if there is evidence of laryngeal oedema. Bronchoscopy is occasionally necessary to remove excessive airway secretions.

Other issues

A detailed history of the circumstances of the exposure will provide important information to guide further management, such as the likelihood of exposure to a poorly soluble gas and the risk of delayed pulmonary oedema or systemic toxicity. Unconscious victims are likely to have received particularly heavy exposures. The circumstances of the exposure may have been psychologically traumatic and panic with psychogenic hyperventilation may need to be identified and managed.

A chest radiograph is essential, but an initially normal film does not rule out the later development of pneumonitis and pulmonary oedema. Patients with significant inhalation injury should be monitored for at least 24 hours. Even if they are well, they should be advised of the risk of delayed pulmonary oedema developing over the next few days, particularly if there has been exposure to low solubility gases such as nitrogen oxides.

Recurrent episodes of pulmonary oedema 1–3 weeks after the initial exposure have been reported following exposure to nitrogen oxides, although the underlying mechanism is obscure. Severe pulmonary oedema should be managed as for the acute respiratory distress syndrome. There is no established role for corticosteroids, but they may help prevent the development of late pulmonary oedema after nitrogen dioxide exposure.

Subacute toxic injury to the respiratory tract

Acute inhalation injuries can give rise to persisting lung damage. Tracheal stenosis, bronchiectasis, asthma, and pulmonary fibrosis have all been reported, but more recently it has become clear that constrictive bronchiolitis is the commonest outcome. Fibrous tissue proliferation with narrowing and obliteration of the small peripheral airways develops as a consequence of respiratory epithelial and basement membrane damage caused by the toxic exposure. Chronic diseases such as chronic obstructive pulmonary disease (COPD) and pneumoconiosis may arise through other 'toxic' or 'irritant' mechanisms (see Chapters 18.8 and 18.13).

Clinical features

Constrictive bronchiolitis following acute inhalation injury

Chronic respiratory symptoms were common in World War I veterans who were exposed to chemical warfare agents, but the underling pathophysiology was poorly characterized. A 10-year follow-up study of those exposed to sulphur mustard in the Iran–Iraq war revealed persisting abnormalities of lung function in almost 50% of subjects. Features of constrictive bronchiolitis were found in two-thirds of a small group of patients who underwent lung biopsy.

The Bhopal disaster of 1984 involved the release of 40 tonnes of methyl isocyanate gas, with at least 3800 immediate deaths. A high proportion of survivors reported ongoing respiratory symptoms and had impaired lung function, probably caused by bronchiolitis.

Persisting constrictive bronchiolitis is also described following acute exposure to other irritant gases including nitrogen oxides, sulphur dioxide, bromine compounds, ammonia, fly ash, and smoke inhalation.

The 2001 destruction of the New York World Trade Centre gave rise to a dense dust cloud of very alkaline pH that caused acute airway and eye irritation and inflammation. 14 000 firefighters were involved, all of whom had pre-exposure lung function measurements. They had a mean fall of FEV1 of 440 ml within the first year of exposure, with little recovery over the subsequent 6 years. The pathological process has been poorly characterized, but biopsy studies have suggested that bronchiolitis is an important mechanism. A range of other outcomes has been reported, including asthma, bronchitis, and sarcoidosis, but a causal relationship with the exposure has not always been clear.

Constrictive bronchiolitis without an antecedent acute injury

Early studies of silo fillers exposed to nitrogen dioxide suggested that some individuals developed insidious-onset constrictive bronchiolitis. A cluster of cases of constrictive bronchiolitis was reported in US military personnel who served in Iraq and Afghanistan and developed persisting breathlessness and exercise limitation. The diagnosis was confirmed by lung biopsy in 38 cases. The commonest association was with proximity to a mine fire that produced high ambient air levels of sulphur dioxide, but one-third of those affected reported no unusual exposures.

Severe constrictive bronchiolitis was identified in eight former workers of a popcorn factory in 2000. Four required lung transplantation. All had handled the butter-flavouring agent 2,3-butanedione (diacetyl), and none had reported work-related symptoms to raise the suspicion of an occupational cause. A subsequent survey of 20 flavouring manufacturing companies identified abnormal lung function in 23% of workers, suggesting a high prevalence of 'popcorn workers lung' (Fig. 18.14.11.2). The disease generally presents insidiously with cough, breathlessness and (in some cases) eye, nose, and throat, and skin irritation. Similar conditions have been reported in other industries with flavouring exposures such as cookie manufacture and coffee processing.

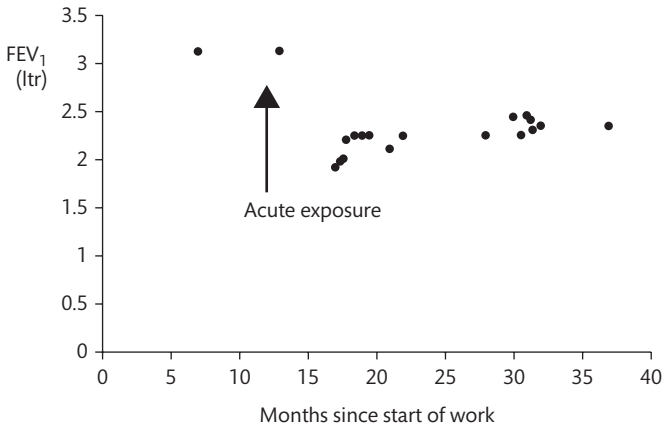

Fig. 18.14.11.2 Lung function in a flavouring manufacturer before and after exposure to diacetyl. Acute irreversible reduction of FEV caused by constrictive bronchiolitis.

Adapted from Hendrick DJ (2008). 'Popcorn worker's lung' in Britain in a man making potato crisp flavouring. *Thorax*, 63, 267–268.

Severe constrictive bronchiolitis has also been described in workers exposed to glass fibre, resins, accelerating agents, and other chemicals when making fibreglass-reinforced boats.

Other subacute lung disease arising from toxic exposures

Outbreaks of respiratory disease have been caused by the inhalation of nylon fragments in the nylon flock industry. Affected workers developed a restrictive ventilatory abnormality with reduced gas diffusion, and interstitial shadowing on chest radiographs or CT scans. Biopsies generally showed a distinctive lymphocytic bronchiolitis and peribronchiolitis with lymphoid hyperplasia and aggregates.

The Ardystil syndrome resulted from an apparently minor change in the formulation of sprayed printing dyes in textile factories. Approximately 10% of exposed workers developed lung disease and 5 of the original case series of 14 patients died. Affected individuals reported breathlessness, cough, and prominent epistaxis. The radiological and pathological appearances were those of organizing pneumonia.

Respiratory problems have been identified in up to 20% of workers exposed to indium in the manufacture of electronic display screens. Radiological abnormalities have often mimicked those of pulmonary alveolar proteinosis, with ground-glass shadowing and superimposed 'crazy paving' interlobular septal thickening. Biopsies showed granular eosinophilic and intra-alveolar exudates typical of pulmonary alveolar proteinosis together with diffuse lung fibrosis.

Diagnosis and management

The recognition of chronic respiratory disease caused by an acute inhalational injury is generally straightforward, but there may be difficulties distinguishing persisting effects of exposure from antecedent lung disease such as asthma or COPD. Disease arising without an acute episode is much more difficult to attribute to the causative exposure. Often effects have been recognized only when a cluster of cases has presented to the same hospital clinic or though detailed epidemiological investigation.

Constrictive bronchiolitis is a particularly difficult diagnosis to establish and is easily mistaken for asthma or COPD. Lung function tests typically show airflow obstruction, but there may be an equal reduction in forced expiratory volume (FEV) and forced vital capacity (FVC) associated with gas trapping and an elevated residual volume. The transfer factor may be normal or impaired. The plain chest radiograph is often normal. High-resolution CT (HRCT) findings may also be subtle, with patchy areas of decreased lung density that are enhanced on expiratory images. Lung biopsies have identified symptomatic disease in the presence of normal HRCT scans and lung function.

Constrictive bronchiolitis generally stabilizes following the cessation of exposure, but there is no clear evidence of benefit from therapy. Those exposed to sulphur mustard have been reported to respond to bronchodilators, inhaled glucocorticoids, oral N-acetylcysteine, and interferon-γ. Popcorn worker's lung does not respond to oral corticosteroids or cyclophosphamide. A high proportion of those with occupationally-induced constrictive bronchiolitis have required lung transplantation.

Importantly, the identification of a sentinel case of possibly work-related disease should prompt a survey of fellow workers and a review of the occupational exposures (see Chapter 10.2.1). Worker education and appropriate surveillance schemes are also important

in the early detection of subacute disease such as bronchiolitis and limiting its adverse consequences.

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18.14.12 Radiation pneumonitis

S.J. Bourke

ESSENTIALS

The lungs can be injured by radiation used in the treatment of cancer, with the rapidly dividing endothelial cells and type II pneumocytes most affected. Immediate injury is followed by an inflammatory response and at a later stage by fibrosis. Chest radiography detects asymptomatic changes in about 50% of patients after radiotherapy. Acute radiation pneumonitis presents with cough, breathlessness, and fever about 2 months after exposure; corticosteroids are usually effective in relieving symptoms but do not prevent the subsequent development of fibrosis. Fibrosis typically develops about 6 months later, may progress for 6 to 24 months, but has usually stabilized by 2 years. Prevention depends on refining techniques for giving radiotherapy.

Introduction

The lungs are vulnerable to injury from radiation used in the treatment of cancers of the lung, breast, oesophagus, spine, thymus, and lymph glands, and when whole-body irradiation is given in preparation for bone marrow transplantation. Radiation pneumonitis continues to cause significant morbidity and rarely mortality, and remains a limiting factor for the intensity of radiation treatment of patients with inoperable lung cancer. It is an important adverse effect which needs to be considered when assessing new treatment strategies using high intensity radiation and concurrent chemotherapy and radiation treatment, particularly in an ageing population with pre-existing lung disease, reduced lung reserve, and comorbidities. Radiation causes direct injury to cells and DNA within the field of radiotherapy, giving rise to pneumonitis and fibrosis. The induction of reactive oxygen species and the initiation of cytokine-mediated inflammatory responses result sporadically in more diffuse radiation lung injury involving areas of the lung outwith the radiotherapy field. Acute radiation pneumonitis is characterized by interstitial inflammation occurring up to 4 months after radiotherapy and then resolving over a matter of weeks or months. Radiation fibrosis, which can occur without preceding pneumonitis, develops about 6 months after radiotherapy and may progress over 6–24 months; it does not resolve, but usually stabilizes by 2 years.

Pathogenesis

Factors which influence the development of radiation pneumonitis and fibrosis include the volume of lung irradiated, the total radiation dose administered, and the dose rate and fractionation. Concomitant use of chemotherapeutic drugs such as taxanes, erlotinib, bleomycin, doxorubicin, methotrexate, and cyclophosphamide can aggravate radiation lung injury. Furthermore, when chemotherapy is given after radiotherapy, 'recall pneumonitis' may develop in the areas of lung previously irradiated. Tamoxifen has been shown to enhance lung injury in patients receiving radiotherapy for breast cancer, which may be due to increased release of transforming growth factor β (TGFβ). Corticosteroid withdrawal may also precipitate radiation pneumonitis, and there is increased risk with pre-existing lung fibrosis or current lung infection.

Absorption of radiation by lung tissues accelerates electrons, generating ion pairs and reactive oxygen species, which damage DNA and produce chemical and biological effects in cells. Rapidly dividing cells, such as endothelial cells and type II pneumocytes, are most affected. The earliest changes involve injury to small vessels with thrombosis, increased permeability, and exudation of protein-rich fluid into the alveoli. Epithelial injury results in sloughing of cells, hyaline membrane formation, and proliferation of type II pneumocytes. Inflammatory cells accumulate in the alveolar walls, followed at a later stage by fibroblasts. Increased plasma concentrations of TGFβ and intercellular adhesion molecule (ICAM)-1 correlate with an increased incidence of radiation pneumonitis. ICAM-1 stimulates the accumulation of inflammatory cells, whereas TGFβ stimulates fibroblast proliferation and induces synthesis of collagen, and genetic polymorphisms that result in high production of TGFβ are associated with more severe radiation fibrosis. Cellular expression of CD95 and CD95-ligand are increased after radiotherapy, and these receptors are involved in the induction of apoptosis, inflammatory cytokine responses, and the attraction of inflammatory cells. These immunologically mediated responses are not confined to the radiotherapy field.

Clinical features

Asymptomatic changes are detectable on a chest radiograph in about 50% of patients after radiotherapy. Characteristically there is an area of opacification that does not show a segmental or lobar distribution: it crosses the normal anatomical structures and is demarcated by a sharp margin corresponding to the limits of the radiotherapy field (Fig. 18.14.12.1). Air bronchograms are often present and there is usually a loss of volume.

Fig. 18.14.12.1 Chest radiograph showing radiation-induced fibrosis, particularly in the right upper zone. Note the sharply demarcated edge to the fibrosis, which does not conform to any normal anatomical structure.

Symptoms occur in about 5–15% of patients, depending on the treatment regimen used, with the onset of cough, breathlessness, and fever about 2 months after radiotherapy. Pre-existing lung disease may increase the clinical impact of radiation pneumonitis, but symptoms often resolve spontaneously. Fibrosis may result in permanent loss of lung function, with a reduction in total lung capacity and carbon monoxide transfer factor associated with chronic breathlessness. This typically develops about 6 months after radiotherapy and may progress for 6–24 months, but has usually stabilized by 2 years.

CT is more sensitive than the chest radiograph in detecting radiation-induced changes such as ground-glass shadowing, septal thickening, and fibrosis, and is useful in differentiating radiation injury from tumour recurrence or infection.

Severe acute reactions to radiotherapy are rare but can occasionally result in respiratory failure and the acute respiratory distress syndrome, particularly in patients with pre-existing interstitial lung disease. Patterns of injury that involve the lungs more diffusely are well recognized. Bilateral lymphocytic alveolitis is often present after unilateral radiotherapy in patients with breast cancer, while positron emission tomography has shown increased metabolic activity in nonirradiated areas of the lung in patients who have had radiotherapy for lung cancer. Diffuse bronchiolitis obliterans organizing pneumonia and chronic eosinophilic pneumonia have also been reported in patients with breast cancer treated by radiotherapy.

Other short-term risks of chest radiotherapy relate to pneumothorax, pleural reactions, and rib fractures, and in the long term there is an increased risk of lung cancer.

Treatment

Most cases of radiation pneumonitis are subclinical or cause only minor symptoms that do not require treatment. In more severe cases corticosteroids are usually effective in relieving symptoms during the acute phase, but they do not prevent the subsequent development of fibrosis. Typically, prednisolone 40–60 mg daily is given until there is clinical improvement, at which stage the dose is tapered while watching for signs of recrudescence of the pneumonitis. Prevention of radiation-induced lung injury is particularly focused on refining techniques which increase the radiation dose delivered to the cancer and reduce exposure of normal lung. Radiotherapy lung injury has been reduced in animal models by the administration of agents such as amifostine, captopril, pentoxifylline, and manganese superoxide dismutase, but a clinical role for these agents has not been established.

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18.14.13 Drug-induced lung disease

S.J. Bourke

ESSENTIALS

Drug-induced lung disease is common and needs to be considered in the differential diagnosis of many respiratory conditions. The nature and timing of events often provide an important clue and are

sometimes sufficiently characteristic for drug-induced lung disease to be diagnosed with confidence, with resolution of symptoms on drug cessation providing further supportive evidence. Well-recognized adverse drug effects are listed in formularies and drug data sheets, but it is often helpful to consult a constantly updated website (http://www.pneumotox.com is highly recommended).

Direct drug effects may arise through toxic, pharmacological, allergic, or idiosyncratic mechanisms, and there may also be indirect effects (e.g. a predisposition to lung infection from cytotoxic and immunosuppressive therapies). From a clinical perspective, adverse effects may be classified according to the induced disorder and the site of involvement.

Asthma is the most common airway disorder to be induced or exacerbated by drugs. It may be produced by a predictable effect related to the drug's pharmacological properties (e.g. β-adrenergic antagonists) or as an idiosyncratic reaction (e.g. aspirin).

Cough is a well-recognized side effect of treatment with angiotensin-converting enzyme inhibitors.

Alveolar and interstitial reactions comprise three main categories: (1) alveolar capillary leakage (e.g. salicylates); (2) interstitial pneumonitis and fibrosis (e.g. bleomycin, amiodarone, infliximab); and (3) pulmonary eosinophilia (e.g. sulphonamides).

Pulmonary vascular involvement includes venous thromboembolism (e.g. oral contraceptive pill), and pulmonary hypertension (e.g. aminorex, now withdrawn), dasatinib, and interferons.

Pleural effusions and thickening may result from drugs (e.g. dantrolene, bromocriptine, methysergide, and dasatinib).

Introduction

Drug-induced lung disease is common and needs to be considered in the differential diagnosis of many respiratory conditions, and in prescribing drugs for the treatment of diseases in all areas of clinical practice. Direct effects may arise through toxic, pharmacological, allergic, or idiosyncratic mechanisms, although often the precise mechanism is unknown. There may also be indirect effects (e.g. a predisposition to lung infection from cytotoxic and immunosuppressive therapies, and the development of respiratory failure from sedation).

Some causes of drug-induced lung disease have now been eradicated (e.g. aminorex pulmonary hypertension) as the causative drug is no longer prescribed. For others, the risks are now so well established that the potential for lung toxicity is considered in the risk–benefit assessment of prescribing (e.g. methotrexate, amiodarone, bleomycin) and the patient is informed of the risks and monitored for the adverse effects. It is for newly introduced drugs that particular vigilance is required: adverse effects must be identified as speedily as possible (e.g. leflunomide, infliximab), early recognition of problems being critical both for the affected individual, so that drug cessation is prompt and the adverse effect is minimized, and also to prevent others coming to harm.

Making the diagnosis of drug-induced lung disease

The first step in diagnosis is to consider the possibility that a clinical presentation might be drug-induced. The nature and timing of events often provides important clues. In some circumstances they are sufficiently characteristic that drug-induced lung disease can be diagnosed with confidence, with subsequent resolution of symptoms on drug cessation providing further supportive evidence. Reintroduction of the drug is rarely indicated unless it is essential in the management of the underlying disease or there is doubt about the diagnosis of an adverse drug effect.

The exclusion of an alternative cause of any clinical events is an important step, with the diagnostic approach adapted to the circumstances of the clinical problem, the likelihood of an adverse drug effect, the possibility of an alternative diagnosis, and the need for a definitive diagnosis to guide management decisions. For example, a patient may develop breathlessness and show diffuse infiltrates on chest radiography when taking immunosuppressive drugs for a connective tissue disease or chemotherapeutic agents for cancer. The clinical features could be due to an adverse drug effect on the lungs, infection, lung involvement by the underlying disease, or the development of coincidental lung disease. Management in these circumstances depends crucially upon accurate diagnosis, and invasive tests such as bronchoscopy, bronchoalveolar lavage, and sometimes lung biopsy may be indicated.

Although well-recognized adverse drug effects are listed in formularies and drug data sheets, the field of drug-induced lung disease is continuously evolving, and it is often helpful to consult a constantly updated website: http://www.pneumotox.com is highly recommended. It is also important to report possible adverse drug reactions to appropriate local authorities, such as the Committee on Safety of Medicines in the United Kingdom, who may also be able to provide information to aid the management of individual cases.

The clinical spectrum of drug-induced lung disease is diverse and complex, and it is therefore advisable to scrutinize the drug list for potential drug causes when patients present with clinical problems for which no other cause is apparent. Drug-induced lung disease may be classified according to the induced disorder and the site of involvement as airways, alveoli/interstitium, pulmonary vasculature, and pleura.

Airways

Asthma

Drug-induced bronchoconstriction may arise by a number of different mechanisms and sometimes the precise mechanism is uncertain. It most often occurs in patients with pre-existing asthma. In some cases the asthma may not have been recognized until an episode of bronchoconstriction occurs as an adverse effect of a drug, but in these instances clues to pre-existing asthma may be apparent when the appropriate history is taken.

Drugs that exacerbate symptoms in subjects with pre-existing asthma may be classified as those that produce an effect which is to some extent predictable from their pharmacological properties, and those which produce bronchoconstriction due to an idiosyncratic effect (Table 18.14.13.1). Less commonly, asthma develops *de novo*, probably because IgE-mediated immunological hypersensitivity has developed. Drug hypersensitivity reactions that include asthma among the manifestations are often associated with blood eosinophilia and/or eosinophilic pneumonia.

Table 18.14.13.1 Drugs that may cause or exacerbate asthma

Pharmacological effects
Cholinergic agents (e.g. carbachol, pilocarpine)
Cholinesterase inhibitors (e.g. pyridostigmine)
Prostaglandin F
Histamine-releasing agents (e.g. curare derivatives, morphine, taxanes)
β-Sympathetic antagonists
ACE inhibitors (cough without asthma more common)
Sensitizing and idiosyncratic effects
Oral
Aspirin and other NSAIDs
Tartrazine-containing preparations
Taxanes (e.g. paclitaxel, docetaxel)
Carbamazepine
Venlafaxine
Parenteral
Penicillin
Iron–dextran complex
Adenosine
Hydrocortisone sodium succinate
N-Acetylcysteine
Inhaled
Nebulized pentamidine, colistin
Inhaled mannitol, hypertonic saline
Eye drops
NSAIDs

ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.

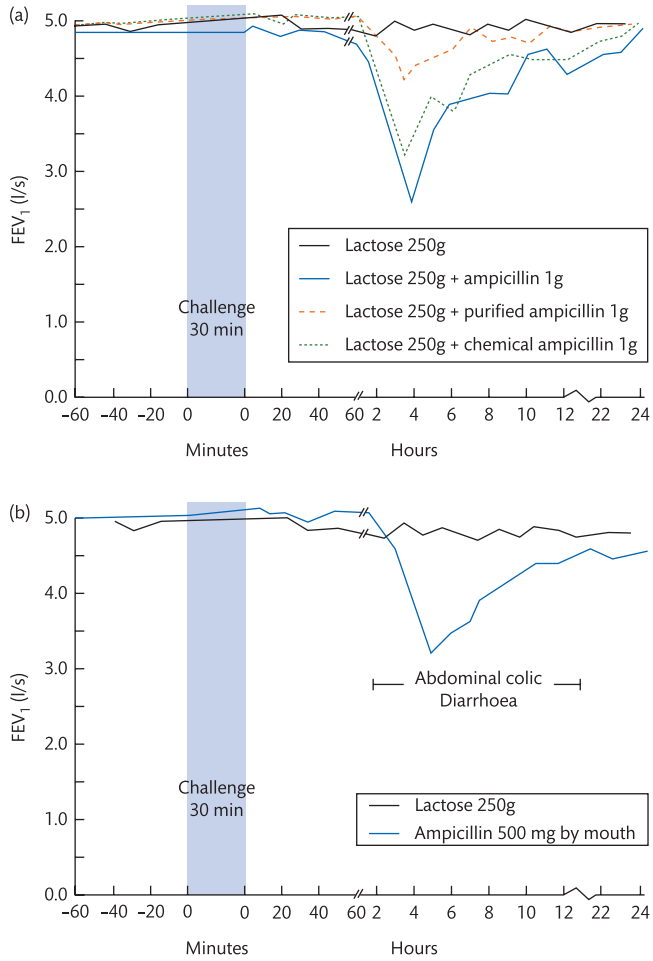

Fig. 18.14.13.1 Results of inhalation and ingestion challenge tests with ampicillin. The inhalation test confirmed that the patient had become sensitized to ampicillin as a consequence of respiratory exposure at work, and the ingestion test showed that asthmatic reactions would be provoked also by oral ingestion at therapeutic dose levels.

Data taken from Davies RJ, Hendrick DJ, Pepys J (1974). Asthma due to inhaled chemical agents: ampicillin, benzyl penicillin, 6-amino-penicillanic acid and related substances. *Clin Allergy*, 4, 227–47.

Drug-induced anaphylaxis

The most dramatic presentation of drug-related bronchoconstriction is as part of an acute anaphylactic reaction; penicillin and intravenously administered iron–dextran are particularly noteworthy among the causal agents. An anaphylactic reaction is characterized by swelling of the tongue, laryngeal oedema, upper airway obstruction, and bronchospasm occurring within minutes of exposure to the drug. Immunological hypersensitivity is presumed to underlie most causes of occupational asthma, some of which involve pharmaceutical agents. Most prominent are certain antibiotics (e.g. cephalosporins, isoniazid, penicillins, piperazine, spiramycin, tetracycline,), the H_2-receptor antagonist cimetidine, the laxative psyllium (ispaghula), pancreatic enzymes, and certain hormones (adrenocorticotropic hormone (ACTH), gonadotropin, pituitary snuff). If an individual sensitized by inhalation in the workplace subsequently uses the relevant drug therapeutically, the potential arises for an asthmatic reaction (Fig. 18.14.13.1). The medical history, when symptoms suggest asthma, should always include details of occupation and medication, and if the patient has ever worked in the pharmaceutical industry the possibility of occupationally induced hypersensitivity to a current medication should be considered.

Cholinergic drugs

Cholinergic drugs, such as carbachol, occasionally produced bronchoconstriction when given systemically, and in very sensitive asthmatic patients exacerbations have occurred after use of pilocarpine eye drops for the treatment of glaucoma. Bronchoconstriction can also occur from the cholinergic effect of pyridostigmine used in the treatment of myasthenia gravis. An inhaled anticholinergic agent has been shown to be effective in reversing occasional untoward effects of cholinesterase inhibitors in asthmatic patients with myasthenia gravis.

β-adrenergic antagonists

β-adrenergic antagonists aggravate bronchoconstriction in patients with asthma. Although drugs, such as sotalol and metoprolol, which target β_1-receptors have less adverse effects on airway function, patients with asthma can still show a reduction in forced expiratory volume in 1 s (FEV_1) or peak flow which can be severe. By contrast, patients with smoking-induced chronic obstructive pulmonary disease often tolerate β-blockers and derive benefit from their use in treating comorbid conditions such as ischaemic heart disease.

Although the adverse effects of oral or systemic β-blockers are well recognized, those of ophthalmic preparations are sometimes

overlooked. Timolol, which is commonly used in eye drops for the treatment of glaucoma, is a potent nonselective β-blocker. Its use has frequently been associated with worsening asthma. The ophthalmic formulation of a newer β-blocker, betaxolol, appears to be less dangerous, but should only be used in patients with asthma if no suitable alternative is available.

Aspirin and nonsteroidal anti-inflammatory drugs

Aspirin and nonsteroidal anti-inflammatory drugs cause bronchoconstriction in about 10% of patients with asthma. This is thought to be caused by a shift of arachidonic acid metabolism away from the cyclooxygenase pathway towards the lipoxygenase pathway, resulting in increased production of leukotrienes which cause bronchoconstriction.

Asthmatic deaths have been reported with both aspirin and indomethacin. These patients often have a triad of nasal polyps, asthma, and aspirin-induced bronchoconstriction. Many patients with analgesic-induced asthma are also sensitive to the azo dye tartrazine, which was a commonly used colouring agent in medications and foodstuffs, and—since it is an approved food and drug additive—its presence is not always declared and hence the extent of the problems it may cause is not clear. In the past tartrazine was present, ironically, in some medications used to treat asthma, but most pharmaceutical companies no longer use it in their formulations.

The importance of drug formulation

Asthmatic symptoms can be a consequence of the particular formulation of a drug or its method of delivery. For example, nebulized solutions of low osmolality can trigger asthmatic reactions if the patient has a high level of airway responsiveness. This appears to have been the main mechanism of bronchoconstriction induced paradoxically by nebulized ipratropium bromide, and since the drug was reformulated in isotonic solution the problem has resolved.

A further cause of bronchoconstriction from nebulized drugs has been the presence of certain preservatives or stabilizers (e.g. benzalkonium chloride, edetate disodium) in the excipient solution. Inhaled antibiotics, such as pentamidine for *Pneumocystis jirovecii* infection, or colistin, tobramycin, or aztreonam for treating bronchiectasis and cystic fibrosis, sometimes also provoke bronchoconstriction. Inhaled mannitol, used as a mucolytic agent in treating patients with cystic fibrosis, is known to provoke bronchoconstriction in patients with asthma and patients should be monitored at the start of treatment with serial spirometry after a trial dose to ensure that they do not develop bronchoconstriction. Prior use of a bronchodilator such as salbutamol is useful in increasing the tolerability of such inhaled medications.

Other drugs that can cause asthma

The bronchoconstrictor prostaglandin $F_{2\alpha}$, used to induce abortion, may be hazardous in asthmatic patients. The occurrence of bronchoconstriction after thiopentone, opiates, and muscle relaxants (tubocurarine, suxamethonium, and pancuronium) is probably due to their capacity to release histamine from basophils. Taxanes, such as paclitaxel or docetaxel, may result in mast cell degranulation, and this can provoke bronchoconstriction. Corticosteroids and antihistamines are therefore routinely given prior to taxane treatment to reduce the occurrence of this adverse effect. Iodinated contrast media used in radiological imaging may activate the complement system, with activation of mast cells and basophils via anaphylatoxins C3a and C5a receptors. Adenosine given intravenously to treat supraventricular tachycardia is a potent constrictor of asthmatic airways. Its effects on the airways are probably due to activation of mast cells via an A2 receptor.

Drug prescribing for patients with asthma

The potential exacerbation of asthma by drugs used to treat it presents a special dilemma, as a drug effect may be difficult to dissociate from spontaneous deterioration. There are well-documented reports of worsening asthma after intravenous hydrocortisone. This is a particular problem in asthmatic patients who also show adverse reactions to aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). The sensitivity to hydrocortisone of these individuals does not extend to other steroids: it appears to be related to the succinate moiety of the hydrocortisone sodium succinate molecule, as it is not seen with the alternative phosphate salt.

Idiosyncrasy probably underlies many asthmatic symptoms related to medication and is the likely explanation for exacerbations following use of intravenous *N*-acetylcysteine in paracetamol poisoning, use of which requires caution in asthmatic patients.

Drugs masking asthma

There are rare situations where cessation of a drug may reveal previously undetected asthma. For example, lithium has been shown to reduce airway responsiveness and inhibit the contractile response of airway smooth muscle, and there are rare reports of asthma becoming apparent for the first time when this medication is discontinued.

Cough

Cough in the absence of asthma is a well-recognized side effect of treatment with angiotensin-converting enzyme (ACE) inhibitors. It develops in 10 to 20% of individuals treated with these drugs and is an effect of the class of drug rather than of specific agents. The cough is nonproductive. There appears to be a weak relation to dose, such that dose reduction may result in some improvement, but in many individuals the symptom remains sufficiently troublesome to necessitate drug withdrawal. Deterioration of pre-existing asthma has also been reported occasionally, but features of asthma are not present in most individuals with cough related to ACE inhibition. The mechanism is unclear; ACE catalyses not only the conversion of angiotensin I to angiotensin II, but also the breakdown of bradykinin and substance P. Since these agents are cough stimulants, their accumulation offers a possible mechanism for this adverse effect. The cough resolves on withdrawal of the drug.

Alveoli and the lung interstitium

Drug-induced alveolar and interstitial lung disease may occur in different clinical settings, with a diverse range of drugs, and encompasses a broad spectrum of disease from acute noncardiogenic pulmonary oedema to insidiously developing pulmonary fibrosis. These conditions are conveniently considered under three main categories: alveolar capillary leakage, interstitial pneumonitis and fibrosis, and pulmonary eosinophilia (Table 18.14.13.2).

Table 18.14.13.2 Alveolar and interstitial drug reactions

Alveolar capillary leakage
Hydrochlorothiazide
Interleukin-2
Naloxone
Opiates
Salicylates
Radiocontrast
Tricyclic antidepressants
Tocolytic agents (e.g. isoxsuprine, terbutaline)
Interstitial pneumonitis and fibrosis
Amiodarone
Antiretroviral therapy
Infliximab
Leflunomide
Methotrexate
Nitrofurantoin
Cytotoxic agents
Azathioprine
Bleomycin
Busulfan
Carmustine (BCNU)
Chlorambucil
Cyclophosphamide
Cytosine arabinoside
Lomustine (CCNU)
Melphalan
6-Mercaptopurine
Mitomycin C
Biological agents
TNFα inhibitors (e.g. infliximab, etanercept, adalimumab)
Monoclonal antibodies (e.g. rituximab, trastuzumab)
Tyrosine kinase inhibitors (e.g. gefitinib, erlotinib)
Interferon α
Pulmonary eosinophilia
Aspirin
Carbamazepine
Chlorpropamide
Dapsone
Gold salts [a]
Imipramine
Methotrexate [a]
Naproxen
Nitrofurantoin [a]
Penicillamine [a]
Penicillins
Phenytoin
Procarbazine [a]
Sulphasalazine
Sulphonamides
Tetracycline

[a] Pulmonary eosinophilia is a feature of some reactions to these drugs, but adverse effects can also occur by other mechanisms.

Alveolar capillary leakage

Acute pulmonary oedema is a recognized complication of overdoses of salicylates, opiates, and tricyclic antidepressants. The pulmonary oedema develops as a result of increased permeability of the alveolar capillary membrane, which is thought to arise through various mechanisms, sometimes involving immunoglobulin and complement deposition in the lung, cytokine release from lymphocytes, and activated neutrophils aggregating and adhering to endothelial cells, releasing toxins, oxygen radicals and mediators (arachidonic acid, histamine, kinins).

Alveolar capillary leakage has also been described with hydrochlorothiazide as an idiosyncratic reaction which does not occur with other thiazide drugs. Acute pulmonary oedema has also been reported with interleukin-2, used in the treatment of melanoma and renal cell carcinoma, and occasionally after injection of radiocontrast media. Infused β_2-adrenergic agonists (terbutaline, isoxsuprine), used as tacolytics to relax the uterus and to inhibit premature labour, may also give rise to florid pulmonary oedema. In these cases there is a close temporal relationship between drug administration and the onset of pulmonary oedema. In other circumstances the acute respiratory distress syndrome may result from a reaction to more prolonged use of drugs including amiodarone, anticancer chemotherapy (vincristine, mitomycin C, melphalan, paclitaxel, cyclophosphamide) and anti-inflammatory drugs (infliximab, methotrexate).

Interstitial pneumonitis and fibrosis

Many drugs may provoke an inflammatory reaction in the lungs with interstitial inflammation, alveolitis, and sometimes fibrosis. Many classic causes are very well-known, but vigilance is required as new drugs are introduced into practice. Early recognition of drug-induced interstitial lung disease allows prompt cessation of the drug.

Interstitial pneumonitis and fibrosis are particularly well recognized with amiodarone, nitrofurantoin, methotrexate, leflunomide, and certain anticancer drugs. When choosing a drug which is recognized to have the potential for lung toxicity, it is important to advise patients of the risk so that they can be alert for the onset of any symptoms. It is also advisable to establish accurately whether the patient has any pre-existing lung disease, and to undertake baseline investigations such as a chest radiograph and lung function tests. This is particularly relevant where the disease being treated is itself associated with interstitial lung disease, as in the case of rheumatoid arthritis and connective tissue diseases.

Clinical presentation and investigation

Patients experiencing a drug-induced pneumonitis may present acutely with cough, fever, shortness of breath, and occasionally systemic upset. Alternatively, there is slowly progressive fibrosis with gradually worsening dyspnoea and widespread shadowing on the chest radiograph. The mechanisms of such reactions are uncertain, but may include toxicity, hypersensitivity, and often idiosyncrasy.

With some drugs—including bleomycin, carmustine, amiodarone, and nitrofurantoin—there is a relation to dose or duration of treatment. Evidence in cases of nitrofurantoin- and bleomycin-induced pneumonitis suggests a role for the production of toxic oxygen radicals in the lungs, perhaps providing a link with the known pulmonary toxicity of oxygen itself and the synergistic adverse effects of high oxygen concentrations and some cytotoxic agents.

A single drug (e.g. amiodarone, methotrexate) may produce a diverse range of histopathological changes in the lungs, including alveolitis, fibrosis, nonspecific interstitial pneumonitis, cryptogenic organizing pneumonia, and diffuse alveolar damage. Lung biopsy therefore tends to show the pattern and severity of interstitial lung disease rather than showing the precise causation, and it is often difficult to establish from biopsy whether fibrosis is due to the underlying disease (rheumatoid or connective tissue lung disease) or a drug reaction. For this reason lung biopsy is of limited value and is rarely performed. Conversely, drugs must always be considered in the differential diagnosis of patients presenting with interstitial lung disease. Histological patterns of nonspecific interstitial pneumonia, usual interstitial pneumonia, and cryptogenic organizing pneumonia have all been associated with many different drugs.

Particular clinical circumstances

Amiodarone

Much interest has centred on the cardiac antiarrhythmic drug amiodarone. It has been estimated that about 6% of patients taking 400 mg or more per day for 2 months or more will develop overt pulmonary toxicity, but there have been several well-documented cases involving smaller doses. The mechanisms may include both immunologically mediated and direct toxic effects. Histologically the lung shows features of chronic inflammation together with interstitial and intra-alveolar fibrosis (**Fig. 18.14.13.2**). Characteristic 'foamy' macrophages are seen, but they are not specific for serious toxic reactions as they are also demonstrable in most patients taking the drug without adverse clinical effects. Occasionally the histological picture is of cryptogenic organizing pneumonia.

Symptoms include progressive dyspnoea, a troublesome cough, and (occasionally) pleuritic pain. Radiographic appearances are varied: most frequently there is a diffuse nodular or alveolar filling pattern, sometimes with upper lobe predominance (**Fig. 18.14.13.3**); sometimes a pleural effusion is present.

The differential diagnoses of amiodarone pulmonary toxicity particularly include left ventricular failure and pneumonia. Measurement of serum brain natriuretic peptide (elevated in cardiac failure) and assessment of left ventricular function by echocardiography is helpful. Bronchoalveolar lavage may be necessary to exclude infection: in amiodarone pulmonary toxicity this typically shows a lymphocytic pattern, but the finding of 'foamy' macrophages is insufficient to confirm the diagnosis. If amiodarone lung toxicity is suspected, cessation of treatment is desirable, but the very long half-life of drug metabolites (many weeks) means that elimination is very slow. Corticosteroids probably suppress the reaction and are often used.

Rheumatoid arthritis

Drug-induced interstitial lung disease is particularly common in the treatment of rheumatoid arthritis and connective tissue diseases. Interstitial disease has been well described in relation to penicillamine, gold salts, and sulphasalazine, but these agents are now much less frequently used than they were in the past.

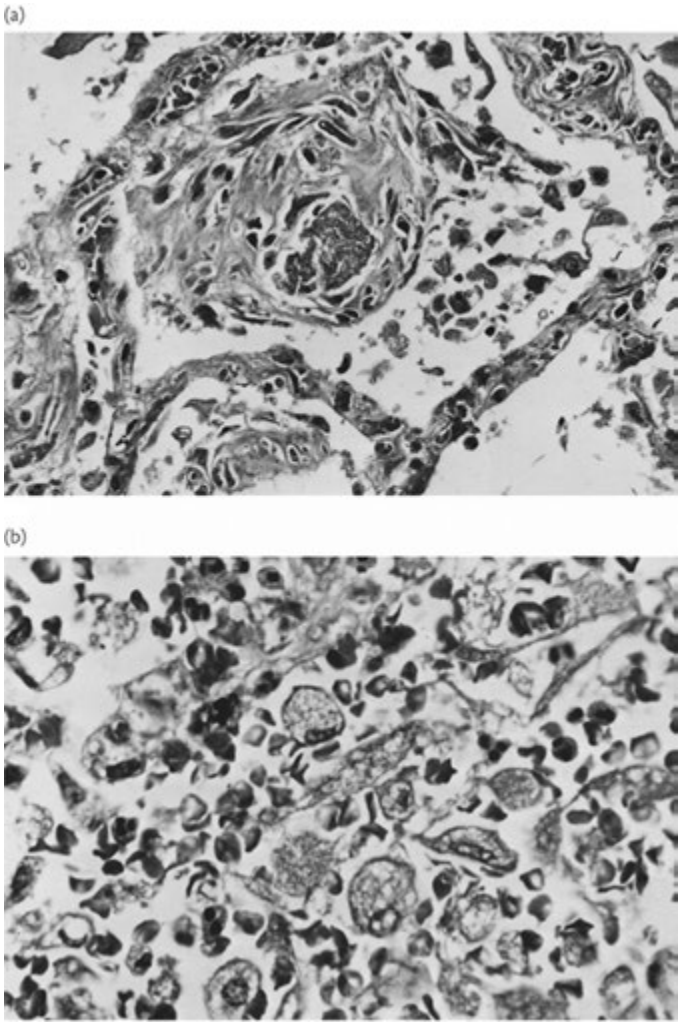

Fig. 18.14.13.2 Histological specimen of the lung of a patient who died from amiodarone pulmonary toxicity, showing (a) alveolar wall thickening and organizing intra-alveolar exudates; and (b) the alveolar exudate with characteristic 'foamy' macrophages, seen at higher magnification.

From Adams PC, *et al.* (1986). Amiodarone pulmonary toxicity: clinical and subclinical features. *Quarterly Journal of Medicine*, 59, 449–71, by permission of Oxford University Press.

Methotrexate is a particularly well recognized cause of drug-induced interstitial lung disease. This is usually a hypersensitivity reaction which is not directly related to the cumulative dose or duration of treatment. Patients typically present subacutely with cough and dyspnoea, sometimes with fever. Chest radiography and CT show diffuse infiltrates. Bronchoalveolar lavage may be helpful in excluding infection and may show a neutrophilic or lymphocytic alveolitis. Lung function tests usually show a reduction in lung volumes and impairment of gas diffusion, but serial monitoring of lung function has not been shown to be helpful in detecting pneumonitis before the onset of symptoms. Where lung biopsies have been performed they have shown a spectrum of interstitial inflammation, fibrosis, type II pneumocyte hyperplasia and (sometimes)

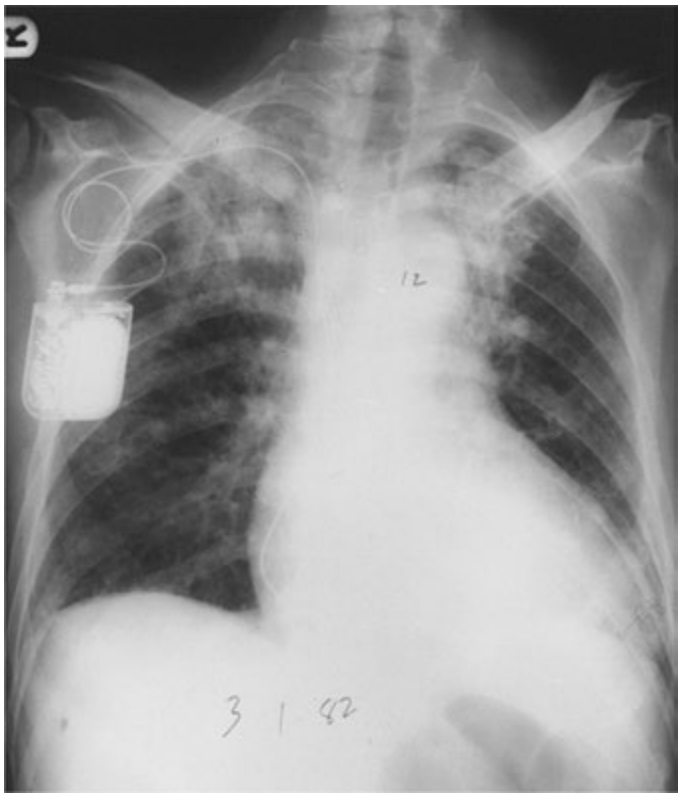

Fig. 18.14.13.3 Chest radiograph of a patient with amiodarone pulmonary toxicity showing confluent alveolar shadowing in both upper lobes.

From Adams PC, *et al*. (1986). Amiodarone pulmonary toxicity: clinical and subclinical features. *Quarterly Journal Medicine*, 59, 449–71, by permission of Oxford University Press.

granulomas. Treatment is by stopping the drug, and corticosteroids are often given.

Leflunomide-induced interstitial pneumonitis is thought to be rare, and the incidence may have been exaggerated by the tendency to use leflunomide rather than methotrexate in patients with pre-existing rheumatoid interstitial lung disease. Nonetheless, it can cause severe pneumonitis, possibly aggravating pre-existing rheumatoid lung disease, such that particular care is required in managing such patients. Leflunomide should be discontinued if there is evidence of new or deteriorating interstitial lung disease, when cholestyramine or activated charcoal can be used to aid elimination of the drug.

Cytotoxic and immunosuppressive drugs

Cytotoxic and immunosuppressive drugs are frequently associated with interstitial pneumonitis. Bleomycin causes problems most frequently, followed by busulfan and mitomycin C. Cyclophosphamide and azathioprine are the most widely used drugs in this group, because of their roles in nonmalignant disease, but produce adverse pulmonary reactions only occasionally. In most cases it is not clear whether the effects are due to direct toxicity or to hypersensitivity.

Bleomycin toxicity is dose-related, occurring more commonly at cumulative doses greater than 300 000 units (European pharmacopoeia units). The recorded frequency of adverse reactions varies with the means by which they are detected, with fibrosis occurring in 5 to 10% of patients treated with busulfan on clinical and functional criteria, but a much higher proportion on the basis of pathological and cytological evidence. Similarly, the increasing use of CT scanning shows an appreciably higher prevalence than found in surveys that employ plain chest radiography. The frequency of overt lung involvement may also be related to length of survival, as determined by the primary disease. With busulfan, the interval between starting treatment and the appearance of toxic effects can be as long as 4 years, and in some cases the lung changes appear to progress after the drug has been discontinued.

With carmustine (BCNU), pulmonary fibrosis may first be recognized several years after treatment has finished. Other factors that may increase the toxicity of a given drug include advanced patient age, and synergism with other drugs, lung radiation, or the subsequent inhalation of high concentrations of oxygen. Histologically, most cytotoxic drugs produce evidence of diffuse alveolar damage with destruction of lining cells, formation of hyaline membranes, and variable degrees of inflammatory infiltration and fibrosis. Fibrosis is particularly common with busulfan and bleomycin, but rare with methotrexate. With methotrexate and procarbazine (and very occasionally with bleomycin) there may be blood and tissue eosinophilia, and correspondingly a good therapeutic response to steroids.

Biological agents

Biological agents are being increasingly used in the treatment of inflammatory conditions and tumours. Certain drug-induced lung conditions have been reported with these agents, and there have also been several reports of interstitial pneumonitis.

Tumour necrosis factor α (TNFα) inhibitors (infliximab, etanercept, adalimumab) are used in the treatment of rheumatoid arthritis and inflammatory bowel disease. Increased susceptibility to respiratory infections, and to tuberculosis in particular, is an important adverse effect, but there have also been several reports of interstitial pneumonitis with these agents.

Monoclonal antibodies (rituximab, trastuzumab) are used in the treatment of some cancers and may cause interstitial pneumonitis. Interstitial pneumonitis has also been reported with tyrosine kinase inhibitors (gefitinib, erlotinib). Interferon-α, used to treat hepatitis C, has been associated with the development of a sarcoid-like granulomatous disease.

The frequency and severity of interstitial lung disease with these different biological agents is not yet well established, but it is important to be alert to possible adverse effects of treatment in patients developing respiratory symptoms on these medications.

Drug-induced sarcoidosis-like reactions

A granulomatous lung disease, mimicking sarcoidosis, has been described after instituting highly active antiretroviral therapy with protease inhibitors in patients with HIV infection. This pattern of lung disease seems to be related to immune reconstitution with enhanced lymphoproliferative responses rather than to any infective organism. Similar drug-induced sarcoidosis-like reactions have also been associated with immune checkpoint inhibitors (e.g. ipilimumab, nivolumab), interferons and TNFalpha antagonists.

Pulmonary eosinophilia

Eosinophilic reactions in the lung include conditions that would be classified as Löffler's syndrome, simple or prolonged pulmonary eosinophilia, and eosinophilic pneumonia (see Chapter 18.14.2).

Tissue eosinophilia is a more consistent feature than peripheral blood eosinophilia. Historically, sulphonamides have been the drugs most frequently reported to cause pulmonary eosinophilia, and sulphonamide sensitivity may also explain some of the reactions to sulphasalazine, which is chemically related. The pulmonary eosinophilia recorded with aspirin appears to be distinct from aspirin-induced asthma. Nitrofurantoin may produce an acute pulmonary eosinophilic reaction in addition to more insidious fibrosis.

The roles of gold salts and penicillamine in eosinophilic reactions have been a matter of some debate, but the evidence suggests that both are involved. It seems unlikely, however, that drugs are responsible for many of the cases of lung fibrosis associated with rheumatoid arthritis. Penicillamine has been incriminated in two other types of adverse pulmonary reaction: (1) pulmonary haemorrhage (Goodpasture's syndrome) when used in high doses for the treatment of Wilson's disease, and (2) obliterative bronchiolitis in patients treated for rheumatoid arthritis.

The clinical severity of eosinophilic reactions is very variable, ranging from a transient and asymptomatic radiographic opacity to a severe eosinophilic pneumonia with dyspnoea, cough, fever, and hypoxaemia. Concomitant asthma is not uncommon. Chest radiography and CT show fluffy opacities, frequently with a peripheral or predominantly upper lobe distribution (Fig. 18.14.13.4). The prognosis is usually good: the changes often subside spontaneously on withdrawal of the drug, while in more severely ill patients there is usually a dramatic improvement on instituting treatment with corticosteroids. Although repeated exposure to the offending agents continues to produce reactions, the severity of these may progressively decrease.

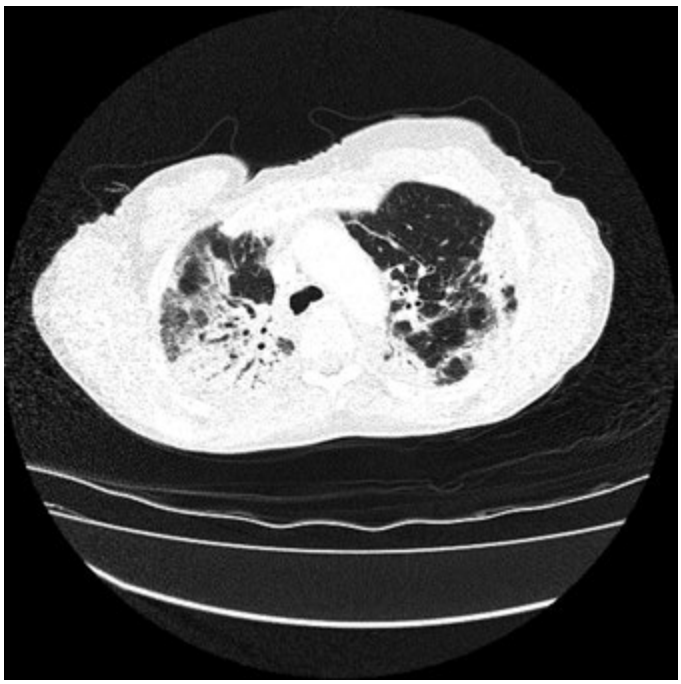

Fig. 18.14.13.4 Eosinophilic pneumonia due to dapsone. CT shows extensive patchy air space opacification in the upper lobes with subpleural predominance. Bronchoalveolar lavage showed eosinophilia and no infection. Blood eosinophil count was elevated at 1.43 × 10^9/litre (0.04–0.4).

Pulmonary vasculature

Several drugs and toxins have been shown to be associated with the development of pulmonary arterial hypertension (Box 18.14.13.1).

Appetite suppressants

In the 1960s there was a major outbreak of pulmonary hypertension in relation to the use of aminorex as an appetite suppressant in Switzerland, Germany and Austria, and the drug was withdrawn. Aminorex resembles adrenaline and ephedrine in its chemical structure.

Fenfluramine and dexfenfluramine were associated with pulmonary hypertension in the 1980s and 1990s. These are serotonin uptake inhibitors and were used also as appetite suppressants. They increase circulating levels of serotonin (5-hydroxy tryptamine, 5HT), which is usually stored in platelets. Serotonin is a direct pulmonary artery vasoconstrictor and promotes growth of smooth muscle. These drugs inhibit the uptake and promote release of serotonin from platelets. Genetic factors seem to be important, and patients who developed pulmonary hypertension on fenfluramine were more likely to be carriers of bone morphogenetic protein type 2 (BMPR2) mutations. Benfluorex was used in France until 2009 and was also shown to be associated with pulmonary hypertension.

Illicit stimulants

Amphetamines, methamphetamines, and cocaine are also considered to be risk factors for pulmonary hypertension based on case reports, epidemiological studies, and pharmacological similarities to fenfluramine. Epidemiological studies showed that patients with idiopathic pulmonary hypertension were 10-fold more likely to have a history of having used these stimulants.

Biological agents

Dasatinib is a tyrosine kinase inhibitor used in the treatment of chronic myelogenous leukaemia. Several reports of pulmonary hypertension have been published in patients receiving this drug. It is thought to act by inhibiting the Src family kinases which play a critical role in smooth muscle cell proliferation and vasoconstriction.

There have also been reports of interferon-α and interferon-β causing pulmonary hypertension.

Box 18.14.13.1 Drugs associated with pulmonary arterial hypertension

Appetite suppressants
- Aminorex
- Fenfluramine, dexfenfluramine
- Benfluorex

Illicit stimulants
- Amphetamines
- Methamphetamine
- Cocaine

Biological agents
- Dasatinib
- Interferon-α, interferon-β

Other drug effects on the pulmonary circulation

Pulmonary thromboembolism related to use of the contraceptive pill is well established; its frequency correlates with the oestrogen content and has been reduced since the introduction of low-oestrogen preparations. Pulmonary veno-occlusive disease has been reported after carmustine (BCNU), mitomycin and bleomycin.

NSAIDs and selective serotonin-reuptake inhibitors are associated with persistent pulmonary hypertension in the newborn. This condition is due to an increased pulmonary vascular resistance that prevents normal pulmonary blood flow and causes a right-to-left shunt through a patent foramen ovale and patent ductus arteriosus. Analgesics given during labour have also been implicated in the development of pulmonary hypertension in the newborn; drugs such as aspirin, indomethacin, and naproxen delay premature labour but, by their inhibitory effects on prostaglandin synthesis, may also cause constriction of the ductus arteriosus leading to pulmonary hypertension *in utero*. This persists into the postpartum period and causes respiratory distress.

Pleura

Some drugs that have been associated with pleural effusions or fibrous thickening are shown in Table 18.14.13.3. Sometimes this arises as part of a syndrome of drug-induced systemic lupus erythematosus (SLE): the antiarrhythmic procainamide was most often implicated, but other agents include gold, hydralazine, isoniazid, penicillamine, captopril, and sulphonamides. When drug-induced SLE affects the respiratory system it particularly involves the pleura, but there is often some fibrosis of the underlying lung.

Practolol, a now obsolete selective β-sympathetic antagonist, produced a characteristic 'oculomucocutaneous' syndrome. This differed from drug-induced SLE in that autoantibodies to histones were not usually present, and ocular symptoms (not usually a feature of drug-induced SLE) were common. Pleural effusions and subsequent pleural thickening occurred in association with characteristic corneal ulceration, discoid rash, and fibrinous peritonitis. Affected patients sometimes developed effusions months or years after discontinuing the drug, and in some the chronic changes led to significant respiratory disability.

Exudative pleural effusions and pleural thickening have been reported with ergot-like drugs, including bromocriptine, cabergoline, ergotamine, methysergide, and pergolide. The pleural effusion may be an isolated manifestation of drug-induced disease or may occur with some lung fibrosis. The precise mechanisms involved are uncertain, but may include hypersensitivity reactions, direct toxic effects, or chemical-induced inflammation. There is a suggestion that previous asbestos exposure may be a promoting factor in some cases. The pleural fluid characteristically contains a high proportion of lymphocytes. The frequency of this reaction is uncertain, but it may be relatively common.

Methotrexate has also been associated with pleurisy, independent of its alveolar effects.

Dasatinib, a tyrosine kinase inhibitor used in the treatment of chronic myelogenous leukaemia, is frequently associated with exudative pleural effusions, possibly by an immune-mediated mechanism.

Eosinophilic pleural effusions have been reported with drugs such as dantrolene, valproate, fluoxetine, propylthiouracil, and sulphasalazine. In these eosinophilic effusions there is usually no evidence of any parenchymal abnormality, and although the changes gradually resolve on withdrawing the drug some residual pleural fibrosis may remain.

Pleuroparenchymal fibroelastosis is a distinctive condition characterized by bilateral apical pleural thickening on chest radiography and CT with breathlessness and restriction of lung volumes. It is often complicated by pneumothorax. There is usually also dense subpleural fibrosis involving the underlying lung parenchyma, with abrupt transition to normal architecture deeper in the lung. It is often idiopathic but has been reported as a late complication of chemotherapy with drugs such as cyclophosphamide and carmustine (BCNU).

Table 18.14.13.3 Drugs associated with pleural effusions and thickening

Clinical presentation	Drug
Drug-induced lupus	Procainamide, etanercept, gold, hydralazine, isoniazid, penicillamine, sulphonamides
Oculomucocutaneous syndrome	Practolol
Isolated pleural effusion	Methysergide, bromocriptine, methotrexate, dantrolene, acebutolol, dasatinib
Pleuroparenchymal fibroelastosis	Cyclophosphamide, carmustine (BCNU)

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