Systemic disease and the lung

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Abstract

Pulmonary manifestations of systemic disease occur in a wide range of conditions, including, most commonly, connective tissue diseases such as scleroderma and rheumatoid arthritis. Certain haematological malignancies are associated with acquired pulmonary alveolar proteinosis. The treatment of myelo-lymphoproliferative diseases with bone marrow transplantation can cause obliterative bronchiolitis as part of a graft-versus-host response. Infectious pathologies such as HIV disease can predispose to opportunistic lung infection, pulmonary lymphoid disorders and cancer. Liver disease occasionally affects the pulmonary circulation, and inflammatory bowel disease the airways. This review will highlight how systemic disease can lead to respiratory manifestations ranging from mild to life-threatening.

Keywords Blood disorders; connective tissue disease; interstitial lung disease; liver disease; systemic disease

Key points

- Lung involvement in systemic disease can manifest as airways disease, interstitial lung disease, pleural complications and/or pulmonary hypertension
- Connective tissue diseases such as scleroderma are the most common systemic diseases to cause chronic pulmonary damage
- Interstitial lung disease and pulmonary hypertension are associated with a worse prognosis in patients with an underlying connective tissue disorder
- Other systemic pathologies associated with pulmonary complications include haematological disorders and their treatment, infectious diseases including HIV, and chronic bowel or liver disease

Introduction

The lung can accumulate damage in many multisystem diseases – the airways, parenchyma, vasculature, pleural membranes and respiratory muscles can all be variably affected by the same underlying systemic process. Multicompartmental respiratory complications can be encountered, for example as interstitial lung disease (ILD) and pleuritis in seropositive rheumatoid arthritis (RA). Treatment of the pulmonary consequences of systemic disease can be targeted specifically to the lung, be targeted generically at the underlying process or be supportive in nature.

Connective tissue diseases (CTDs)

CTDs can occur as 'pure' entities or overlap syndromes in which the clinical features include aspects of different entities (e.g. scleroderma and Sjögren's syndrome). CTD–ILD is most commonly encountered in RA, scleroderma and the myositides. Patients with CTD–ILD are more likely to be female and younger than those with idiopathic ILD. In recent years, the use of biological response modifiers ('biologics') has been extended from treating the underlying CTD to targeting the lung disease.

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Scleroderma

The best studied of all the CTDs with a predilection for lung disease is scleroderma. The most common radiological pattern of scleroderma-associated ILD is non-specific interstitial pneumonia (NSIP) (Figure 1). ILD is more common in diffuse cutaneous scleroderma, in which the presence of anti-Scl-70 antibodies is associated with more severe systemic disease and a worse prognosis.

Conversely, pulmonary hypertension (PH) is more common in limited cutaneous scleroderma, in which the presence of anticentromere antibody is positive in 50–90% of cases. The development of ILD and PH significantly worsens the prognosis of patients with scleroderma. Oesophageal dilatation and dysmotility in this condition can promote reflux of gastric contents that can cause additional lung injury. Recognized but unlicensed therapies for scleroderma-associated ILD include cyclophosphamide, mycophenolate and prednisolone (unlicensed use in the UK, although mycophenolate carries NICE guidance for use).

Rheumatoid arthritis

Fibrotic ILD, pleural thickening or effusions and pulmonary nodules represent the more common pulmonary manifestations of this disease. Male gender and cigarette smoking have been associated with a greater risk of developing RA-ILD, with usual interstitial pneumonia (UIP) being the most commonly seen pattern. RA-ILD and antibodies against cyclic citrullinated peptides may be detected before the development of the articular aspects of RA.

Evidence for the use of specific therapies in RA-ILD is lacking, but corticosteroids, cyclophosphamide and mycophenolate mofetil have been used off-licence with varying effectiveness. Several drugs used in treating the underlying RA, including methotrexate and sulfasalazine, can rarely induce iatrogenic pneumonitis.

Idiopathic inflammatory myositides (IIM)

This heterogeneous group of disorders includes dermatomyositis (Figure 2), polymyositis and either dermatomyositis- or

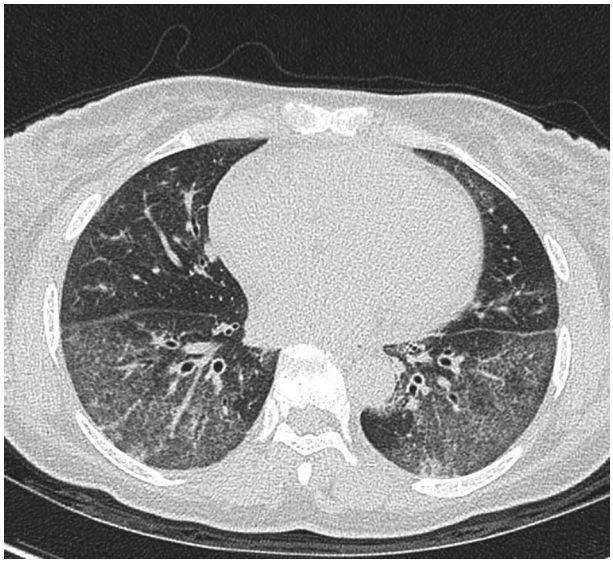

Figure 1 Computed tomography image of the lung showing fibrotic non-specific interstitial pneumonia changes caused by underlying connective tissue disease.

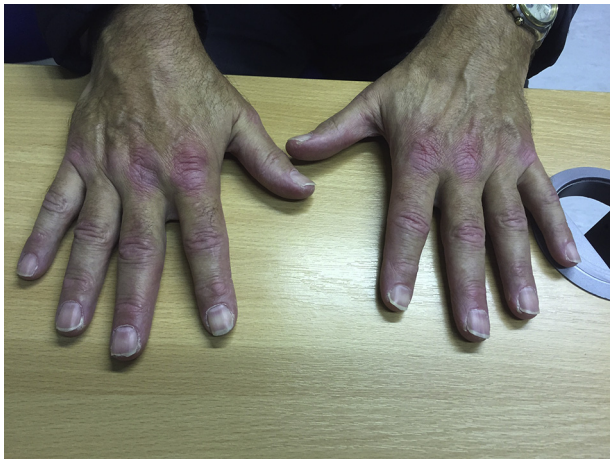

Figure 2 Gottron's papules in a patient with dermatomyositis.

polymyositis-predominant disease in conjunction with circulating antibodies against aminoacyl-tRNA synthetase (forming anti-synthetase syndrome).

Around 30—40% of individuals with IIM develop ILD at some stage in their disease, most commonly as organizing pneumonia (OP), NSIP or UIP. ILD can precede, accompany or follow the presentation of muscle disease. A small proportion of patients present with fulminant diffuse alveolar damage with life-threatening respiratory failure. Pure respiratory muscle weakness is rare in IIM, but an increased risk of malignancy including lung cancer is recognized.

Autoantibodies present in IIM are either myositis-specific antibodies or myositis-associated antibodies. Anti-Jo-1 targeting the histidyl moiety of a tRNA synthetase is a myositis-specific antibody, whereas anti-Ro (anti-Sjögren's-syndrome-related antigen A) and anti-La (SSB) antibodies are examples of myositis-associated antibodies as they are also found in non-myositis CTDs.

Patients with IIM tend to respond well to immunosuppression, particularly with corticosteroids. Other treatments (unlicensed in the UK) include mycophenylate, tacrolimus and rituximab, a chimeric monoclonal antibody targeting the CD20 protein on the B cells.

Systemic lupus erythematosus (SLE)

SLE is a great clinical mimic with wide-ranging pulmonary consequences. In general, SLE-associated pleural involvement is more common than parenchymal lung disease. Overall, ILD also occurs less often in SLE than in other CTDs. The term 'lupus pneumonitis' describes an acute/subacute syndrome of lung injury associated with a high mortality risk.

Although haemoptysis can be occult, radiological abnormalities typically include a combination of diffuse alveolar damage and diffuse pulmonary haemorrhage. Shrinking lung syndrome, characterized principally by ventilatory restriction, is also described in SLE. Its pathogenic basis is poorly understood. Finally, the presence of lupus anticoagulant increases the rate of thromboembolic phenomena including pulmonary embolism.

Vasculitis

The vasculitides are categorized by the size of blood vessel involved and the presence of anti-neutrophil cytoplasmic antibody (ANCA) (Table 1).

Diffuse alveolar haemorrhage is the most dramatic pulmonary manifestation of vasculitis. Its most common identifiable cause is Wegener's granulomatosis (WG), also known as granulomatosis with polyangiitis.

Non-haemorrhagic manifestations of pulmonary vasculitis include diffuse parenchymal disease conforming to the radiological and histological patterns of UIP (Figure 3), NSIP or mixed NSIP/OP. Pulmonary vasculitic nodules, most commonly described in WG, have a tendency to cavitate and produce

Vasculitides characterized by mechanism

Mechanism	Immunofluorescence staining pattern	Examples of clinical syndromes
Immune complex deposition-mediated	Granular	Systemic lupus erythematosus, Henoch—Schönlein purpura, essential cryoglobulinaemia
Anti-neutrophil cytoplasmic antibody antibody-associated	Negative	Wegener's granulomatosis, Churg—Strauss syndrome, microscopic polyangitis
Anti-glomerular basement membrane antibody-associated	Linear	Goodpasture's syndrome

Table 1