

REVIEWS

Imaging of the pulmonary manifestations of systemic disease

A G Rockall, D Rickards, P J Shaw

Department of Radiology, University College London Hospitals, London, UK
A G Rockall
D Rickards
P J Shaw

Correspondence to:
Dr A Rockall,
Department of Academic Radiology, St Bartholomew's Hospital, Dominion House, St Bartholomew's Close, London EC1A 7BE, UK

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Lung involvement in systemic disease may be a manifestation of the underlying pathological process, may be a complication of the underlying disease or may be related to the treatment. Lung pathology is dominant in certain diseases, such as in Wegener's granulomatosis, but may be only rarely present, for example in Henoch-Schönlein purpura. However, lung involvement has a profound effect on prognosis and may be challenging to accurately diagnose. In some patients, bronchoalveolar lavage and tissue diagnosis with transbronchial or percutaneous biopsy is not possible, due to the poor clinical state of the patient.

Imaging often plays a central part when lung involvement is suspected clinically and this role has increased with the advent of high resolution computed tomography (HRCT). The chest radiograph may provide diagnostic information and be useful in follow up but it is relatively insensitive. HRCT now has several established roles:

(1) May be diagnostic and if not will often narrow the differential diagnosis.^{1,2} This in turn may reduce the need for biopsy.³ The HRCT signs of interstitial lung disease, small airways disease and bronchiectasis are well established (see box 1).

(2) May demonstrate pathology when the chest radiograph appears normal, in patients with respiratory symptoms or abnormal pulmonary function tests. This particularly applies to diseases in which the radiographic signs are subtle or obscured by overlying structures, for example obliterative bronchiolitis, bronchiectasis, early fibrosing alveolitis, and fine walled cystic structures, such as in lymphangiomyomatosis.

(3) Assessment of disease activity. Several studies suggest that ground glass shadowing on HRCT in fibrosing alveolitis corresponds histologically to active alveolitis.⁴ This in turn predicts a better response to treatment⁵ and better prognosis.⁶ Although ground glass shadowing is non-specific, it often represents reversible pathology, such as infection, haemorrhage, or oedema.

(4) Assessment of interval change and treatment response, by acquiring comparative scans on follow up.

(5) Prognostic information.

(6) Planning a biopsy: for example transbronchial biopsy in peribronchial disease or percutaneous in subpleural disease and in guiding the optimal site for open biopsy, by defining areas of active alveolitis and avoiding areas of established fibrosis.

Box 1: HRCT signs (adapted from Webb *et al*²³ p 118, 207, 243)

Fibrosing alveolitis

1. Findings of fibrosis: intralobular interstitial thickening, irregular interfaces, visible intralobular bronchioles, honeycombing, traction bronchiectasis.*
2. Irregular interlobular septal thickening.
3. Ground glass opacity.
4. Peripheral and subpleural predominance of abnormalities.*†
5. Lower lung zone and posterior predominance.*†

Bronchiectasis

1. Bronchial dilatation.*†
2. Bronchial wall thickening.*†
3. Visibility of peripheral airways.*†
4. Contour abnormalities *†—for example, signet ring (vertically orientated bronchi), tram tracks (horizontally orientated bronchi), loss of tapering.
5. Fluid filled bronchi.*†
6. Atelectasis.

Bronchiolitis obliterans organising pneumonia (BOOP)

1. Patchy bilateral airspace consolidation.*
2. Ground glass opacity.*
3. Subpleural and/or peribronchovascular distribution.*
4. Bronchial wall thickening, dilatation in abnormal areas.*
5. Small nodular opacities, often peribronchiolar.
6. Combination of findings 1 and 2.*†

Obliterative bronchiolitis

1. Areas of decreased lung opacity, patchy in distribution.*
2. Bronchiectasis.*
3. Attenuation of pulmonary vessels.*
4. Combination of 1-3.†
5. Areas of consolidation or increased lung opacity.
6. Reticulonodular opacities.

*Most common findings; †findings most helpful in differential diagnosis

(7) Prospective HRCT studies may help in understanding the natural history of lung involvement in systemic disease.

Recently, several groups have published HRCT findings in several of the systemic diseases. This evidence based article reviews the radiological features of lung involvement, including the recent literature on HRCT

Box 2: Pleuropulmonary manifestations of rheumatoid arthritis

Pleural

- Pleuritis/pleural thickening.*
- Pleural effusion.*
- Empyema.
- Pneumothorax.

Parenchymal

- Interstitial lung disease.*
- Nodules.
- Caplan's syndrome.

Airways

- Bronchiectasis.*
- Bronchiolitis obliterans organising pneumonia (BOOP).
- Obliterative bronchiolitis.
- Bronchocentric granulomatosis.
- Follicular bronchiolitis.

Pulmonary vasculitis/hypertension

Drug induced lung disease

Amyloidosis

*Most common findings

appearances, in the connective tissue diseases, systemic vasculitides and miscellaneous systemic diseases with lung involvement.

* * *

Section A: connective tissue diseases

RHEUMATOID ARTHRITIS

The lungs, heart, and the vascular endothelium may be involved in rheumatoid arthritis. There is a strong association with a positive rheumatoid factor when systemic manifestations or vasculitis are present. *Pulmonary involvement* (box 2) is significant prognostically. In a large autopsy study, Tyoshina *et al* reported that lung involvement was second to infection as the most common cause of death (18% *v* 27%).⁷

Pleural disease

Pleural disease is common in postmortem studies (40%–75%)^{8,9} and is associated with subcutaneous nodules, interstitial lung disease and pericarditis, in middle aged men with high rheumatoid factor titres.^{9–11} Effusions, seen in 3%–5%,^{9,12} usually occur at periods of active arthritis but may precede the arthritis.¹³ They are usually small, unilateral¹⁴ and asymptomatic, with mild pain in 20%–28%.¹⁵ They often resolve over weeks but may be persistent and recurrent.¹⁶ Pleural thickening is seen on chest radiography in 20%.¹⁷ Analysis of the pleural fluid may be helpful diagnostically.¹⁸ Pneumothorax and empyema are unusual findings^{19,20} and may be secondary to cavitation of a necrobiotic nodule. A spontaneous sterile empyema may develop during active rheumatoid arthritis.¹⁹

Parenchymal disease

Interstitial lung disease—The association of fibrosis and rheumatoid arthritis (RA-ILD) is well established. The prevalence varies depending on the diagnostic criteria: chest radiograph abnormalities occur in 1%–6%^{11,12,18,21};



Figure 1 Chest radiograph of a 60 year old man, with rheumatoid arthritis and progressive dyspnoea, showing signs of fibrosing alveolitis with basal volume loss and reticular opacities, more pronounced on the right (courtesy of Dr H Booth).

pulmonary function test abnormalities in 40%^{11,22}; and histological changes in 80% of patients, including some asymptomatic patients with a normal chest radiograph.²³

There is a male preponderance (2M:1F) with an insidious onset in the 50s, with a cough and/or dyspnoea. Patients are usually seropositive, with established joint disease in 90%, and have subcutaneous nodules and finger clubbing.¹¹ Over 70% of patients are smokers.

The appearances on chest radiography are indistinguishable from cryptogenic fibrosing alveolitis, with bibasal reticular, reticulonodular, or honeycomb interstitial opacities and progressive volume loss but may be asymmetric (fig 1).^{12,21} Pleural abnormalities and pulmonary nodules, if present, may help to distinguish RA-ILD from cryptogenic fibrosing alveolitis.¹¹

HRCT demonstrates interstitial lung disease in patients with and without clinical evidence of the disease (69%–80% and 20%–29%).^{21,24} The signs are those of cryptogenic fibrosing alveolitis (fig 2, box 2).^{18,21,25} Follow up HRCT demonstrates progressive honeycombing from the lung bases towards the apices.²¹ Emphysema and bronchiectasis have been reported in association with RA-ILD, including non-smoking patients.^{24–26}

Diffuse interstitial pulmonary amyloidosis may mimic interstitial lung disease and should be considered in the differential diagnosis in cases with longstanding rheumatoid arthritis.²⁷

Computed tomography is used to direct biopsy towards areas of presumed active alveolitis (ground glass areas). Histology is often mixed, including interstitial pneumonitis, bronchiolitis obliterans organising pneumonia (BOOP), lymphocytic interstitial pneumonitis, lymphoid hyperplasia, and rheumatoid nodules.¹⁸ The features are similar to cryptogenic fibrosing alveolitis except for an increase in lymphoid follicles, which is suggestive of RA-ILD or the presence of rheumatoid nodules (pathognomonic for rheumatoid arthritis).

The course of RA-ILD is variable, usually being slowly progressive, and pulmonary hypertension may develop. The prognosis is poorer than in nodular disease or BOOP.¹⁸

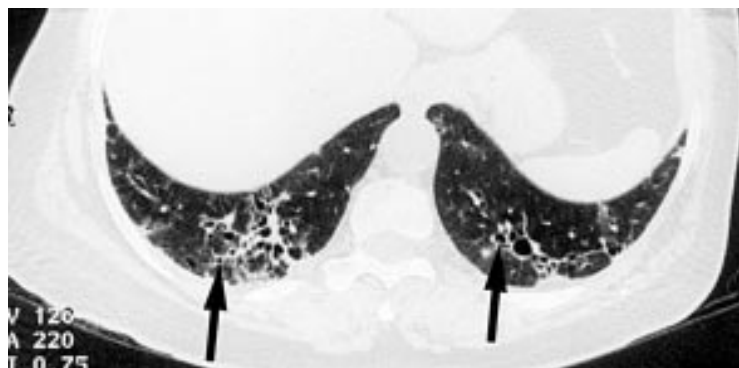


Figure 2 A 66 year old woman with rheumatoid arthritis. HRCT demonstrates peripheral basal fibrosis with architectural distortion and traction bronchiectasis (arrows) (courtesy of Dr H Booth).

Pulmonary nodules—Rheumatoid nodules are more common in men, usually in smokers with subcutaneous nodules, and high rheumatoid factor titres.¹¹ Patients are usually asymptomatic, although large nodules may rupture into the pleural space.^{11 19–21} The appearance of nodules does not necessarily reflect overall disease activity¹¹ and may antedate the onset of arthritis.^{9 28 29} Histologically, they are identical to subcutaneous nodules and are pathognomonic of rheumatoid arthritis.¹⁴

Nodules are identified in less than 1% of chest radiographs,⁹ in 22% on computed tomography,²¹ but are seen pathologically in 32.5%.³⁰ Radiographic features of rheumatoid arthritis nodules are non-specific being located subpleurally, usually multiple and range from a few millimetres to several centimetres in diameter.^{11 21 30 31} Cavitation, occurring in approximately 50%, may be associated with pneumothorax, pleural effusion, or empyema after rupture into the pleural space; calcification is rare.

Nodules cause diagnostic problems, raising the possibility of a primary or secondary malignancy.^{13 32} They have been reported to take up radio-iodine³³ and fluorine-18-fluorodeoxyglucose in positron emission tomography imaging.³⁴ Regression, with time or during treatment (with steroids) may be helpful in the diagnosis, as rheumatoid arthritis nodules usually run a benign course. However, cytological/histological confirmation is advocated by some authors³¹ particularly as lymphoma and lung cancer are reported to occur with a higher incidence in rheumatoid arthritis.³⁵

Caplan's syndrome—The association of rheumatoid arthritis with pulmonary nodules and coal miner's pneumoconiosis was first described by Caplan in 1953,³⁶ with a similar syndrome reported with other inorganic dusts such as silica and asbestosis.⁹ Peripheral, well defined, solitary or multiple nodules often appear rapidly in crops at times of increased rheumatoid arthritis activity and are often associated with new subcutaneous nodules. Biopsy reveals inorganic dust within the necrotic nodule. The nodules are asymptomatic and do not require treatment unless a complication develops following rupture of a cavitating lesion into the pleural space.³⁶

Airways disease

A strong association between rheumatoid arthritis and airways disease has been demonstrated on pulmonary function tests.³⁷ Geddes *et al* found that 38% of patients with a normal chest radiograph had airflow obstruction.³⁷ One explanation for this is recurrent chest infections but small airways disease has been demonstrated histologically with no history of chest infections or smoking.³⁸

Radiologically, bronchiectasis in rheumatoid arthritis has been described in several series and may precede the onset of rheumatoid arthritis.^{21 39 40} It may be secondary to interstitial fibrosis (traction bronchiectasis) or isolated.⁴⁰ Although insensitive, the commonest chest radiograph appearance is of bibasal linear markings and focal infiltrates.³⁹ On computed tomography, bronchiectasis and bronchiolectasis have been demonstrated in 30% of unselected patients.²¹ On HRCT, peribronchovascular micronodules, forming a "tree-in-bud" appearance, in non-smokers may correspond to small airways disease (see box 1). Interestingly, HRCT features of small airways disease was noted in 20 of 33 patients with normal pulmonary function tests suggesting that HRCT is more sensitive than these tests.⁴⁰ In this study, 70% of patients were smokers.

BOOP—May be seen in rheumatoid arthritis, affecting middle aged women with established seropositive rheumatoid arthritis.¹⁴ Histologically, there is a proliferative bronchiolitis with intraluminal granulation tissue in the distal bronchioles, alveolar ducts, and alveoli.⁴¹ Presentation is non-specific (subacute onset of cough, dyspnoea, and low grade fever), with restrictive pulmonary function tests and a reduced diffusion capacity. The chest radiograph shows bilateral, patchy, peripheral, ill defined alveolar/acinar or linear opacities. HRCT additionally demonstrates ground glass opacities and small nodular opacities in a peribronchial and peribronchiolar distribution and bronchial wall thickening.⁴² Infection must be ruled out and empirical treatment with antibiotics is often used. Diagnosis is by biopsy. There is a good response and prognosis with steroids.^{41 43 44}

Obliterative bronchiolitis—This is rare and may occur as a primary feature of rheumatoid arthritis or secondary to drug therapy such as D-penicillamine. It carries a poor prognosis.⁴⁵ It usually affects women with well established rheumatoid arthritis and positive rheumatoid factor, who present with a dry cough and rapidly progressive dyspnoea. There are reduced breath sounds and faint basal crackles. Pulmonary function tests demonstrate airflow limitation with an increased total lung capacity and preserved diffusion capacity. Histology demonstrates intense inflammation and obliteration of the terminal and respiratory bronchioles with sparing of the alveoli.⁴⁶

The chest radiography may be normal, over-inflated, or infrequently demonstrate patchy interstitial lung disease (fig 3A). HRCT demonstrates a mosaic attenuation pattern, with marked inhomogeneity of lung density in adjacent pulmonary lobules, in a geometrical

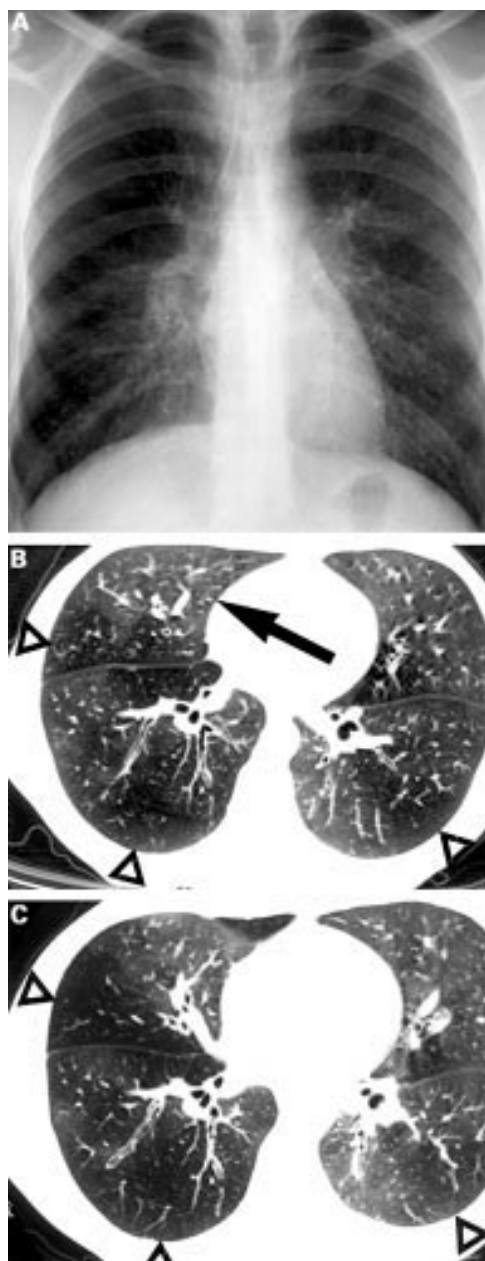


Figure 3 A 37 year old markedly dyspnoeic man with rheumatoid arthritis. (A) Chest radiograph demonstrates reduced vascularity in the right upper zone and bronchial wall thickening in the lower lobes. The suspected diagnosis was obliterative bronchiolitis. (B) HRCT in inspiration demonstrates a mosaic attenuation pattern with normal parenchyma (arrow) and extensive areas of reduced vascularity (arrowheads), highly suggestive of obliterative bronchiolitis. (C) HRCT in expiration confirms the diagnosis by demonstrating air trapping in the areas of reduced vascularity (arrowheads).

pattern (fig 3B, box 1).⁴⁶ Expiratory scans confirm air trapping (fig 3C).

Bronchocentric granulomatosis—This is a granulomatous inflammation of the airways, usually associated with asthma and aspergillus and, rarely, associated with rheumatoid arthritis.^{47 48} Presentation is with dyspnoea, cough, haemoptysis, and chest pain. Imaging reveals unilateral or bilateral nodules, measuring several centimetres, possibly with cavitation, which are bronchocentric in distribution on

computed tomography. Histologically the features are similar to rheumatoid arthritis nodules. Nodules may remain static or resolve with steroids.⁴⁷

Follicular bronchiolitis is lymphoid follicular hyperplasia along the airways. It is seen uncommonly and probably manifests as reticulonodular opacities on chest radiography.³⁰

Pulmonary vasculitis

Pulmonary vasculitis, rarely seen in rheumatoid arthritis, may occur with a systemic vasculitic process with cutaneous and renal involvement or, less commonly, is isolated to the lungs.⁴⁹ Histology demonstrates a necrotising vasculitis affecting small to medium sized arteries or rarely, a necrotising capillaritis with immune complex deposition.⁴⁹

Patients present with dyspnoea, cough, occasionally haemoptysis or acute respiratory failure.^{11 49} The chest radiograph may be normal, demonstrate interstitial opacities or signs of pulmonary hypertension (enlarged central pulmonary vessels with peripheral pruning).¹¹ In rare cases of diffuse alveolar haemorrhage, focal or diffuse alveolar opacification may be seen.⁴⁹

Drug induced pulmonary disease

Drug induced lung disease from methotrexate, gold, and D-penicillamine is difficult to diagnose, with no pathognomonic features. Other diagnoses must be excluded, particularly infection.

Methotrexate pneumonitis is a potentially serious condition with a prevalence of between 0.3% and 18%, with a mean of 3.3% in an extensive review by Salaffi *et al.*⁵⁰ Patients with pre-existing lung disease (such as interstitial lung disease or asthma), older age, diabetes, and smokers are at greater risk and are usually rheumatoid factor positive.^{14 50} Presentation may be subacute, with dyspnoea, dry cough, fever, malaise and occasionally chest pain, with hypoxia.

The chest radiograph demonstrates diffuse bilateral usually basal interstitial or alveolar infiltrates.⁵⁰ Lymphadenopathy and pleural effusions may suggest the diagnosis.^{51 52} Computed tomography demonstrates heterogeneous ground glass opacities and septal lines.⁵⁰

Bronchoalveolar lavage excludes infection, particularly *Pneumocystis carinii* pneumonia, which may have similar clinical and radiological features and may complicate low dose methotrexate therapy.⁵³

Gold induced pulmonary disease, usually an interstitial pneumonitis, has been rarely reported and is difficult to diagnose. A total of 140 reported cases were reviewed to assess the features which help to differentiate gold induced interstitial lung disease from RA-ILD and are female preponderance (6:1), low titres of rheumatoid factor, absence of subcutaneous nodules and finger clubbing, and the presence of fever and skin rash.⁵⁴ The presenting symptoms were of dyspnoea, dry cough, fever, and occasionally cyanosis.

Box 3: Pleuropulmonary manifestations of SLE*Pleural*

- Pleuritis.*
- Effusions.*

Parenchymal

- Interstitial fibrosis.*
- Acute lupus pneumonitis.
- Diffuse alveolar haemorrhage.
- Lymphocytic interstitial pneumonia.

Airways

- Bronchiectasis.
- BOOP.
- Obliterative bronchiolitis.

Other (uncommon)

- Pulmonary thromboembolic disease.
- Pulmonary artery hypertension.
- Pulmonary vasculitis.
- Acute reversible hypoxaemia.

Secondary features

- Infection* (conventional or opportunistic).
- Atelectasis/respiratory muscle dysfunction.
- Related to cardiac or renal failure.
- Drug or oxygen toxicity.

*Most common findings

The chest radiograph shows diffuse interstitial infiltrates. Computed tomography demonstrates bronchocentric alveolar opacities, which may be helpful, as the changes from RA-ILD are predominantly peripheral. Cysts and high attenuation nodules may be seen in a subpleural distribution.⁵⁴

Treatment of methotrexate pneumonitis and gold induced interstitial lung disease and discontinuation of the drug usually results in a very good response clinically and radiologically but fatalities have been reported.^{51 53 54}

D-penicillamine has been associated with interstitial lung disease and it may cause an obliterative bronchiolitis with significant morbidity and mortality and therefore drug withdrawal together with aggressive treatment may be required.¹⁴

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

This type III immune complex disease is characterised by inflammatory changes in connective tissues, blood vessels, and serosal surfaces. It affects women of childbearing age (F:M =10:1) and is more common in black women (3:1), presenting with widely diverse clinical manifestations.

Pulmonary involvement

The lungs are commonly involved (box 3), although there are wide variations in the reported prevalence depending on criteria: series based on clinical findings report an incidence of 50%–70%¹¹; pulmonary function tests demonstrate 88% of unselected patients having a reduced diffusion capacity.⁵⁵ In this same series, abnormal chest radiography was noted in 38% of patients. At autopsy, pleuroparenchymal changes attributable to SLE were

found in 22% of patients. Pulmonary changes related to infection (44%), cardiac or renal failure, or oxygen toxicity were also found.⁵⁶

Clinical manifestations include cough, dyspnoea and pleuritic chest pain, the latter being accompanied by fever.^{11 57 58}

Lupus pleuritis/effusions

Pleuritis is the commonest pleuropulmonary manifestation, occurring in 30%–60% of patients at some stage, usually in established disease and usually associated with pain and pleural effusions.^{59 60} Effusions are usually bilateral and small. Residual pleural thickening may occur and is reported in up to 70% of chest radiographs of symptomatic patients⁵⁷ but is unusual in asymptomatic patients.⁶¹

On HRCT, pleural and pericardial thickening or irregularity were reported in 13% of asymptomatic patients, 24% of unselected patients, and in 87% of patients with respiratory symptoms.^{57 61 62}

Pleural fluid is a serous or serosanguinous exudate and immunological analysis helps in the differential diagnosis.⁶³ Effusions may be secondary and an infective aetiology must be excluded. They usually resolve spontaneously, although corticosteroids provide rapid symptomatic relief.⁵⁹

Parenchymal disease

Interstitial fibrosis—Only 1%–6% of patients have evidence of interstitial lung disease clinically or on chest radiography.^{61 64 65} The prevalence is higher in autopsy studies⁶⁶ and on HRCT, with signs of interstitial lung disease seen in 60% of symptomatic patients,⁵⁷ in 38% of asymptomatic patients with normal chest radiography,⁶¹ and in 32% of unselected patients.⁶⁷

The chest radiography and HRCT signs are similar to those of cryptogenic fibrosing alveolitis.⁵⁷ In one HRCT study, nine of 11 patients with an abnormal HRCT were asymptomatic, seven had a normal chest radiograph, and four had normal pulmonary function tests.⁶⁷ This increased sensitivity of HRCT for the detection of early interstitial lung disease has also been found with rheumatoid arthritis²⁴ and systemic sclerosis.⁶⁸ Interstitial lung disease usually follows an insidious course but may lead to respiratory failure.

Acute lupus pneumonitis—This is uncommon but life threatening, with an estimated incidence of 1%–4%.⁶⁴ The diagnosis is one of exclusion from infection, acute pulmonary oedema, haemorrhage, or infarction. Patients are extremely ill, with fever, tachypnoea, and hypoxia. The chest radiograph reveals ill defined, bilateral patchy air space consolidation in a peripheral, basal distribution, which rarely cavitates. There may be an effusion.¹¹ A normal chest radiograph does not exclude the diagnosis.⁶⁹ On HRCT, ground glass opacities have been attributed to acute lupus pneumonitis, but there is limited biopsy correlation.⁵⁷

Histology demonstrates diffuse alveolar damage and interstitial oedema. An incomplete

response to treatment carries a high mortality.^{69 70} Clinical resolution is usually accompanied by complete radiographic clearing.

Airways disease

Airways disease in SLE, rarely identified on chest radiography, has been reported at autopsy. Gross *et al* found distal airways disease in all lung specimens and bronchiolar dilatation in 36% of specimens.⁷¹ HRCT demonstrates bronchiectasis or bronchial wall thickening in 20%–35% and centrilobular tree-in-bud opacities.^{57 61 67} Increased susceptibility to infection may be the underlying cause of bronchiectasis.⁶⁷

BOOP—This has rarely been reported with SLE, both during the course of the illness or as a presenting feature.^{42 72} There is usually a good response to steroids. The differential diagnosis includes infection and acute lupus pneumonitis.

Pulmonary haemorrhage and vascular disease

Diffuse alveolar haemorrhage—Asymptomatic pulmonary haemorrhage is a common autopsy finding⁶⁶ and may be secondary to aspiration, congestive cardiac failure, renal failure, infection, and acute lupus pneumonitis.^{56 73} Acute diffuse alveolar haemorrhage is uncommon but occurs in SLE more frequently than in other connective tissue diseases.⁷⁴ This is a potentially fatal complication of SLE, with a mortality rate of approximately 60%.^{73 75} Presentation is with dyspnoea, anaemia, and haemoptysis (in 42%–66%).⁷³ In a series of 510 hospital admissions for SLE, 3.7% had diffuse alveolar haemorrhage and in 80% of these patients, pulmonary capillaritis was the cause.⁷³ Differentiation between diffuse alveolar haemorrhage due to pulmonary capillaritis and other causes often requires lung biopsy. The histology is a diffuse alveolitis secondary to an immune complex capillaritis.

The chest radiograph findings are bilateral diffuse or patchy air space or reticulonodular opacities, usually sparing the apices, which may be migratory, and appear and resolve rapidly.⁷⁶ Magnetic resonance has been reported to help diagnostically by demonstrating the signal characteristics of blood.⁷⁷

Pulmonary hypertension—This is uncommon, seen in approximately 5%–14%.^{78 79} It is usually primary but may be secondary to recurrent thromboemboli, a complication of interstitial lung disease or a feature of SLE mixed connective tissue disease overlap syndrome. Cavitating consolidation may be seen in pulmonary infarction. Pulmonary hypertension in SLE is associated with antiphospholipid antibodies⁸⁰ and the prognosis is variable.⁵⁹

Rarities

Lymphocytic interstitial pneumonia, pseudolymphoma, obliterative bronchiolitis, acute reversible hypoxaemia, and hilar adenopathy are rarely seen.^{58 81 82} Pulmonary vasculitis is rare but may be the cause of a cavitating nodule.⁸³

Secondary changes

Infection—This is the commonest pleuropulmonary manifestation, accounting for approximately 50% of pleuropulmonary disease and is the commonest cause of parenchymal opacities radiographically.^{11 15 66 81} Infection may be life threatening, particularly with immunosuppressive treatment or renal failure. In one large autopsy series, 44% of patients had bronchopneumonia, 8% had aspiration pneumonia, and 7% had an opportunistic infection, including fungal and pneumocystis pneumonia.⁵⁶ An infective aetiology should always be excluded before diagnosing primary SLE related lung disease.

Diaphragm dysfunction/atelectasis—An elevated diaphragm and basal atelectasis in the absence of parenchymal abnormalities have been attributed to a diffuse diaphragmatic myopathy.^{84 85} This restrictive disorder presents with dyspnoea, and often orthopnoea, a symptom experienced by patients with diaphragmatic paralysis.⁸⁴ Atelectasis may be secondary to pulmonary embolic disease or diaphragmatic splinting from painful pleuritis.

Pulmonary oedema may be secondary to renal or cardiac failure. Fluffy alveolar shadowing in the perihilar region and lower zones occurs with or without pleural effusions. The differential includes infection and acute lupus pneumonitis.

Drug induced lupus

Approximately 5%–10% of patients with drug induced SLE (commonly with procainamide and hydralazine) have lung disease, with pleural and pericardial effusions being the commonest manifestation. Prognosis is good once the drug is discontinued.⁸⁶

SJÖGREN'S SYNDROME

This autoimmune syndrome is characterised by lymphocytic infiltration of the lacrimal and salivary glands. Other exocrine glands and extraglandular sites may be involved (in 5%–10%⁸⁷). The syndrome may be primary or secondary, being associated with another autoimmune disease, commonly rheumatoid arthritis. It affects women (F:M = 9:1) over the age of 40.

Pulmonary involvement (box 4)—This is estimated between 9%–90%^{88–90} depending on diagnostic criteria and patient selection. Symptoms include persistent cough, dyspnoea, and recurrent chest infections.^{11 89} In secondary Sjögren's, pulmonary features may be dominated by the associated connective tissue disease, with interstitial lung disease and less frequently, pleural disease.^{91 92} In primary Sjögren's, pulmonary function tests, and HRCT have demonstrated that interstitial lung disease and small airways disease are common.^{93 94} Interstitial lung disease may be due to fibrosing alveolitis (8%–33%^{90 95}) or lymphocytic interstitial pneumonitis, which is found in 0.9%–42%.^{90 96} Airways disease is also multifactorial: tracheobronchial desiccation leads to inspissated mucous and recurrent chest infections⁹²; lymphocytic infiltration of the airways causes a follicular lymphocytic

Box 4: Pulmonary manifestations of Sjögren's syndrome*Airways*

- Tracheobronchial desiccation and recurrent infection.*
- Bronchiectasis.*
- Small airways disease.*

*Interstitial fibrosis***Pleural disease†*

- Pleuritis.
- Pleural thickening/effusion.

Lymphoproliferative

- Lymphocytic interstitial pneumonitis.
- Pseudolymphoma.
- Lymphoma.

*Most common findings; †in secondary Sjögren's

bronchitis in up to 31%.⁹⁵ Lymphoproliferation, with mass-like aggregates of benign lymphocytes (pseudolymphoma) or lymphoma,⁸⁷ usually non-Hodgkin's, may occur. Lymphoma is more frequent in primary Sjögren's, usually in the salivary glands, but is also reported in the lungs, in 1%–2%.^{91 94 97} Rarities include BOOP,⁹⁸ pulmonary amyloidosis,⁹⁹ and pulmonary hypertension.¹⁰⁰ The prognosis of pulmonary disease associated with primary Sjögren's is good unless a lymphoma develops.⁹²

Radiological features

Chest radiography—Changes are reported in 5.5%–14%.^{94 101} Basal reticular or reticulonodular opacities are seen in interstitial lung disease (fibrosing alveolitis or lymphocytic interstitial pneumonitis),^{94 102} although associated air space shadowing is suggestive of lymphocytic interstitial pneumonitis.¹⁰³ Bronchiectasis and pleural effusions^{11 89 91} are reported in studies which included both primary and secondary Sjögren's. Enlarging mediastinal nodes and multiple nodular/air space opacities may indicate pseudolymphoma or lymphoma.^{89 91 94 104}

HRCT—Findings in primary Sjögren's syndrome have been reported in non-smoking, predominantly asymptomatic patients.^{94 101} HRCT demonstrated abnormalities in 28%–34%. The commonest findings were small airways disease (bronchiolectasis, bronchial wall thickening, tree-in-bud appearance, and air trapping) and signs of fibrosing alveolitis.^{94 101} One case with alveolar consolidation was confirmed as lymphoma. HRCT abnormalities occurred in 19% of asymptomatic patients.⁹⁴ This concurs with bronchoalveolar lavage findings, in primary Sjögren's, of subclinical alveolar inflammation in 55%.¹⁰⁵

POLYMYOSITIS/DERMATOMYOSITIS (PM/DM)

This inflammatory condition of skeletal muscle and skin may be associated with another connective tissue disease or a neoplasm.¹⁰⁶ It affects females (F:M = 2:1) in the 30–60 age group.¹¹ Systemic manifestations include arthropathy, pulmonary or cardiac disease.

Box 5: Pulmonary manifestations of PM/DM

- Aspiration pneumonia secondary to dysphagia.*
- Fibrosing alveolitis.*
- BOOP.*
- Diffuse alveolar damage.
- Pneumonia/opportunistic infections.
- Malignancy, primary or metastatic.
- Ventilatory insufficiency secondary to muscular weakness.

*Most common findings

Pulmonary involvement—This occurs in up to 50% of patients^{107 108} and is associated with significant morbidity and mortality.¹⁰⁸ The pulmonary manifestations are listed in box 5.

Aspiration pneumonia—Aspiration pneumonia secondary to dysphagia is common (15%–20%) and potentially fatal.¹⁰⁸ There is an impaired cough reflex due to muscle weakness involving the pharynx and oesophagus.¹⁰⁹ Chest radiography demonstrates segmental air space consolidation in dependent areas.

Interstitial lung disease—This has a reported prevalence of 5%–30% depending on diagnostic criteria.^{107 108 110} It may present concurrently, after, or, in up to a third of cases, before the diagnosis of PM/DM.^{111 112} Presentation is commonly with insidious progressive dyspnoea but may be acute, or asymptomatic with abnormal chest radiography and pulmonary function tests.

Common histological patterns are BOOP, fibrosing alveolitis, and diffuse alveolar damage.¹¹³ Histology is helpful in predicting prognosis, BOOP having a relatively favourable prognosis compared with fibrosing alveolitis, with a uniformly poor prognosis in diffuse alveolar damage. However, there is a significant post-biopsy mortality and treatment is rarely altered.¹¹³

Chest radiography—The pattern is similar to cryptogenic fibrosing alveolitis, with basal reticular or reticulonodular opacities or mixed alveolar/ground glass and interstitial opacities.¹¹³ Progressive honeycombing may occur. BOOP and diffuse alveolar damage result in bilateral air space consolidation.

HRCT—HRCT appearances of PM/DM have been described.^{112 114 115} Basal subpleural ground glass and linear opacities were seen in over 90% of patients who underwent computed tomography. Mid to lower zone patchy consolidation in subpleural or peribronchial regions, seen in 50%–100% of cases, usually correlated with BOOP where histology was available.¹¹² These patients generally improved with steroid therapy, although honeycombing was occasionally seen on follow up.¹¹⁴ Diffuse alveolar damage was confirmed in a patient with diffuse ground glass and consolidation.¹¹² Overall, peripheral air space consolidation and peribronchial thickening are fairly characteristic of pulmonary involvement in PM/DM and there is a relatively lower incidence of honeycombing.^{114 115} HRCT may prove to be of help in

Box 6: Pulmonary manifestations of PSS

112 122–124 224 225

- Interstitial fibrosis.*
- Oesophageal dilatation*/aspiration pneumonia.*
- Pulmonary hypertension.*
- Infection.
- Mediastinal lymphadenopathy.
- Pleural thickening.
- Pleural and pericardial effusions.
- Diffuse alveolar haemorrhage.

*Most common findings

predicting histology, assessing disease progression, and monitoring response to therapy.^{112 114 116}

Malignancy—There is a higher than expected incidence of neoplastic disease, particularly lung carcinoma, with a higher rate mortality from cancer in patients with dermatomyositis.¹¹⁷ Symptoms of PM/DM may predate the tumour by one to two years.

Respiratory muscle dysfunction—Respiratory muscle dysfunction resulting in respiratory failure is unusual (under 5%) but minor impairment occurs more commonly, with recurrent pneumonia or mucous plugging.¹⁰⁸ Chest radiography demonstrates elevated hemidiaphragms and basal atelectasis.

Rarities—These include pulmonary hypertension¹¹⁸ and pulmonary vasculitis/capillaritis with diffuse alveolar haemorrhage.¹¹⁹

PROGRESSIVE SYSTEMIC SCLEROSIS (PSS)

There is inflammation, fibrosis, and vascular changes in the skin, resulting in scleroderma, with variable multisystem involvement of other internal organs, usually affecting women in their 50s to 60s. Three clinical subgroups have been described²⁰: (1) classical PSS; (2) CREST syndrome; and (3) overlap syndromes in which PSS coexists with another connective tissue disease such as rheumatoid arthritis, SLE, or PM/DM.

Pulmonary involvement—This is prevalent (box 6) with changes in 74%–95% in autopsy studies and is a significant cause of morbidity and mortality, with exertional dyspnoea reported in a third of patients.⁶⁸ Pulmonary involvement is less common with the CREST syndrome.^{121 122}

Interstitial fibrosis—This is the commonest manifestation, present in 20%–65%.^{68 123} Restrictive pulmonary function tests with a decreased diffusing capacity may precede clinical or radiographic changes.^{11 122}

Chest radiography—Changes, present in up to 65%, are of cryptogenic fibrosing alveolitis (fig 4A) with progression from fine to coarse reticular opacities and honeycombing.^{68 123} Cystic lesions may result in spontaneous pneumothorax.¹¹

HRCT—This detects pulmonary abnormalities in 60%–91% of patients.^{68 122 124 125} The signs are those of cryptogenic fibrosing alveolitis (fig 4B).^{68 122 124} Subpleural cysts are noted in 17% of adults.⁶⁸ Consolidation or masses are uncommon.¹²²

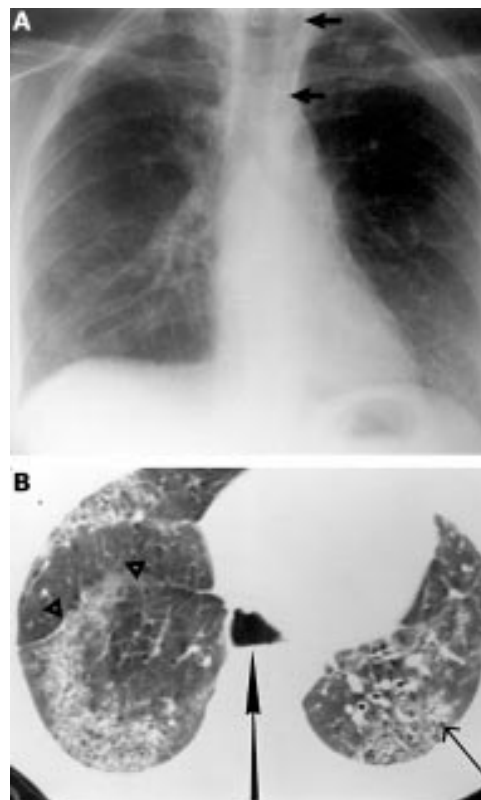


Figure 4 A 35 year old patient with PSS and dyspnoea. (A) Chest radiograph demonstrates bibasal symmetrical fine reticular opacities of fibrosing alveolitis with volume loss on the right and a dilated oesophagus (arrows). Incidental, old apical tuberculous disease. (B) HRCT demonstrates ground glass shadowing, architectural distortion with irregularity of the right oblique fissure (arrowheads), reticular opacities, and traction bronchiolectasis (small arrow). The dilated oesophagus is also noted (large arrow).

Oesophageal dilatation—This is common and useful diagnostically, as the signs of interstitial fibrosis are indistinguishable from cryptogenic fibrosing alveolitis. Aspiration pneumonia may occur.¹²⁶

Pulmonary hypertension—This is usually secondary to interstitial lung disease but may be primary.^{127 128} It is relatively common, seen in 50% of patients with CREST and 33% of patients with classical PSS at angiography.¹²⁹ Chest radiography is less sensitive but is very specific, with enlargement of the main pulmonary arteries and cardiomegaly.^{121 124 129}

Diffuse pleural thickening—This is seen in 20% on HRCT.¹²² Significant effusions are uncommon.^{11 121}

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

MCTD has overlapping features of SLE, PSS, and PM/DM and increased titres of antiribonucleoprotein antibody, affecting women in their 30s to 50s. Lung involvement (box 7) occurs in up to 80%¹³⁰ and may be detected on chest radiography or pulmonary function tests in 69% of asymptomatic patients.^{130–132} Manifestations are similar to those of SLE, PSS, and PM/DM.^{131 132}

Interstitial lung disease—This is similar to the pattern of SLE, PSS, and PM/DM and is the commonest abnormality seen on chest radiography, seen in 21%–85%.^{131 133} Thirty per cent

Box 7: Pleuropulmonary manifestations of MCTD

- Interstitial fibrosis.*
- Pleuritis*/pleural effusion/thickening.
- Pulmonary arterial hypertension.*
- Aspiration secondary to oesophageal dysmotility.
- Pulmonary thromboemboli.
- Diffuse alveolar haemorrhage.
- Neuromuscular respiratory failure.
- Mediastinal lymphadenopathy.

*Most common findings

Box 8: Common pleuropulmonary manifestations of ankylosing spondylitis*Changes of spondyloarthritis*

- Ankylosis of costovertebral joints.*
- Reduced chest wall mobility.*

Pulmonary

- Apical fibrobullous disease* +/- mycetoma.

*Most common findings

of patients have signs of interstitial lung disease on chest radiography at presentation.¹³¹ Histologically the appearances are of fibrosing alveolitis.

Pleural disease—This is common, with pleuritic chest pain in 40% but radiographic signs of thickening and effusions are less common.^{131 133}

Pulmonary arterial hypertension—This has an insidious onset but may be rapidly progressive carrying significant morbidity and mortality.¹³¹ It is usually a primary vascular process due to intimal proliferation and medial hypertrophy of small arterioles but may be secondary to interstitial lung disease or chronic pulmonary emboli. The chest radiograph may be normal or have characteristic changes.

Oesophageal dysmotility—This is common (74%) and may cause aspiration pneumonia.^{131 133}

Diffuse alveolar haemorrhage—This has been reported and may occur with a systemic vasculitis or rarely with isolated pulmonary capillaritis.^{49 134}

ANKYLOSING SPONDYLITIS

This seronegative arthropathy may have extra-articular manifestations including ocular, cardiac, and pulmonary disease.

Pulmonary involvement (box 8)—This is reported in 1.3%–15%.^{62 135} Patients are usually asymptomatic but may present with cough, dyspnoea, and rarely haemoptysis (from tuberculous or fungal colonisation⁶²). Limitation of chest expansion, caused by ankylosis of the costovertebral joints, is common.¹³⁶ Pulmonary function tests may be restrictive or less commonly obstructive.⁶²

Chest radiography—Findings in 2080 patients with ankylosing spondylitis are reported by Rosenow *et al.*¹³⁵ Twenty six patients (1.3%)

had apical fibrosis/fibrobullous disease (resulting in gross distortion and hilar retraction), five had mycetoma formation, three had pleural effusions, two had pneumothoraces, and two had signs of cor pulmonale. Tracheobronchomegaly (Mounier-Kuhn syndrome) has been reported.¹³⁷

HRCT—This demonstrates abnormalities in 69%–71%, including interlobular septal thickening, basal interstitial lung disease, bronchiectasis (primary and traction), emphysema, upper lobe fibrosis, pleural thickening, mycetoma formation, and mediastinal lymphadenopathy.^{62 138} The patients with basal interstitial lung disease had respiratory symptoms and abnormal pulmonary function tests typical of fibrosing alveolitis and no interstitial changes on chest radiography. Two patients had saber sheath trachea and two had increased tracheal dimensions with proximal bronchiectasis.

Thus, HRCT demonstrates a more extensive spectrum of pulmonary pathology compared with chest radiography.

RELAPSING POLYCHONDROITIS

Relapsing polychondritis is a rare systemic condition of unknown aetiology with recurrent, progressive inflammation and destruction of cartilage, commonly involving auricular, laryngeal, tracheobronchial, and nasal cartilage.^{139–141}

Up to a third of patients have another autoimmune disease.^{140 142 143} Presentation is in the 40 to 60 age group (M=F) with no familial predisposition.^{139 140}

Airways manifestations

Airways involvement usually presents with cough, dyspnoea, hoarseness, localised tenderness, and recurrent pneumonia. It is common (56%–70%) and may carry a poor prognosis, causing approximately 50% of deaths.^{139 144} However, a recent study found a lower prevalence of airways disease, with few life threatening manifestations,¹⁴⁰ possibly due to earlier diagnosis and improved treatments. Initially, airways narrowing may be due to mucosal oedema, but subsequent destruction of cartilage results in increased collapsibility with fixed airway narrowing secondary to fibrosis.

Radiological appearances

Although tracheal narrowing may be evident on the chest radiograph, computed tomography has a major role in establishing the diagnosis and in assessing response to therapy.^{145 146} Narrowing of the trachea and main bronchi is usually continuous, although more focal areas of stenosis are reported.^{146 147} Multiple tracheal cartilages may appear expanded and calcified, due to cartilage hypertrophy and new bone formation.^{145 147} Calcification may occur following steroid therapy.¹⁴⁸ Involvement of the ears and nose help diagnostically.

HRCT may demonstrate bronchiectasis in segmental and subsegmental bronchi, with mucous plugging and bronchial wall thickening, possibly due to recurrent pneumonia secondary to proximal obstruction.^{145 147}

Table 1 Nomenclature of major systemic vasculitides. Adapted table of Chapel Hill Consensus Conference^{149, 153*}, with permission

	G/NG */+	Vessel type and additional characteristics	Frequency of pulmonary involvement*
Small vessel vasculitis			
Wegener's granulomatosis	G/*	Respiratory tract involvement and vasculitis of small to medium sized vessels	90%
Churg-Strauss syndrome	G/*	Eosinophil-rich, granulomatous inflammation of respiratory tract and vasculitis of small to medium sized vessels, associated with asthma and eosinophilia	70%
Microscopic polyangiitis	NG/*	Few or no immune deposits, vasculitis affecting small vessels	50%
Henoch-Schönlein purpura	NG/+	IgA dominant immune complexes affecting small vessels	<5%
Essential cryoglobulinaemic vasculitis	NG/+	Cryoglobulin immune depositis, affecting small vessels	<5%
Medium vessel vasculitis			
Polyarteritis nodosa	NG	Medium and small arteries involved; no vasculitis in arterioles, capillaries or venules	
Kawasaki disease	NG	Arteritis of large, medium and small arteries, associated with mucocutaneous lymph nodes	
Large vessel vasculitis			
Giant cell (temporal) arteritis	G	Aorta and branches: >50 years Temporal artery	
Takayasu arteritis	G	Aorta and branches: <50 years	

G = granulomatous; NG = non-granulomatous; *indicates ANCA association; +indicates immune complex association.

The differential diagnosis includes sarcoid, Wegener's granulomatosis, amyloidosis, and infectious perichondritis.¹⁴⁶

* * *

B. Systemic vasculitides

The aetiology and clinical manifestations of the vasculitides are diverse, leading to difficulties in nomenclature and diagnostic criteria. The Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides proposed a classification based on vessel size, further refined by other distinguishing features, such as granulomatous inflammation or eosinophils.¹⁴⁹ We have used this classification (table 1). Certain vasculitic diseases are associated with immune complex deposition and others with antineutrophil cytoplasmic antibodies (ANCA). The incidence of systemic vasculitis in the UK has been reported as 42 per million per year¹⁵⁰ with 50% of cases being ANCA positive.

Pulmonary vasculitis may occur in the context of a primary systemic vasculitis or may be associated with an underlying disease (box 9). Pulmonary involvement is frequent in the ANCA positive small vessel vasculitides and Goodpasture's syndrome but is less common in the immune complex vasculitides.

SMALL VESSEL VASCULITIS

It is critically important to recognise and treat small vessel vasculitis early to prevent irreversible end organ damage, which may be fatal from acute pulmonary haemorrhage or tracheobronchial involvement. The previously high mortality rate has been dramatically reduced by early therapy, with improvement in 90% and complete remission in 75% in Wegener's granulomatosis.¹⁵¹ Lung biopsy may contribute to patient mortality.¹⁵²

Wegener's granulomatosis

The classic triad includes pulmonary granulomatous inflammation, systemic small vessel vasculitis, and glomerulonephritis. During the course of the illness, 90% have upper respiratory tract disease and 85% have pulmonary disease, with symptoms of cough, mild dyspnoea, chest pain, and haemoptysis. A third of patients may be asymptomatic, despite having

abnormalities on chest radiography.^{151, 152} Patients without renal involvement are termed "limited Wegener's granulomatosis". Wegener's granulomatosis is strongly associated with cANCA.¹⁵³ Pathologically, a necrotising vasculitis affects vessels of all size, with granulomatous inflammation in pulmonary nodules.

Radiological features

Pulmonary nodules—A review of 77 patients with biopsy proved Wegener's granulomatosis demonstrated pulmonary nodules, on chest radiography and/or computed tomography, in 69%.¹⁵² These were well defined, irregular, and commonly bilateral varying in size from 5 to 100 mm (fig 5A). Half were cavitated, with thick walls. Air fluid levels were uncommon. Nodules were generally multiple, but less than 10 and increased in size and number and became cavitated during the course of untreated disease.^{152, 154} A computed tomography study demonstrated nodules in 88% of patients and noted scarring, spiculation, and pleural tags emanating from nodules as well as distinct feeding vessels¹⁵⁵ (fig 5B). Peripheral wedge shaped lesions were also described, similar to pulmonary infarcts. After treatment, there may

Box 9. Pulmonary vasculitides^{153, 226}

Pulmonary involvement as part of a systemic vasculitis

- Wegener's granulomatosis.*
- Churg-Strauss syndrome.*
- Microscopic polyangiitis.*
- Goodpasture's syndrome.*
- Behçet's disease.*
- Henoch-Schönlein purpura.
- Essential cryoglobulinaemic vasculitis.
- Takayasu's disease.
- Giant cell (temporal) arteritis.

Pulmonary involvement in a vasculitis associated with a systemic disease

- Connective tissue disease* (for example, SLE, rheumatoid arthritis, PSS).
- Paraneoplastic.
- Bronchocentric granulomatosis. Inflammatory bowel disease.
- Drug induced vasculitis.

*Most common findings

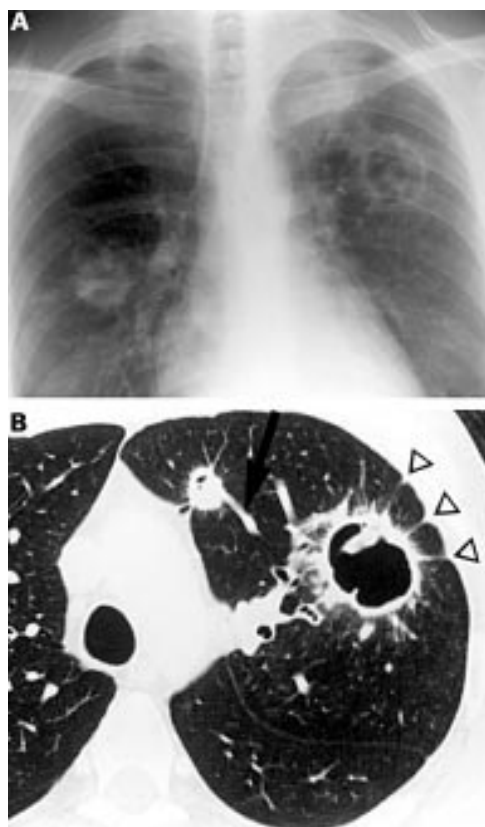


Figure 5 (A) A 35 year old man with Wegener's granulomatosis. The chest radiograph demonstrates multiple, bilateral cavitating nodules and a left apical mass. (B) HRCT demonstrates a thick walled cavitating mass in the left upper lobe with spiculation and pleural tags (arrowheads). A feeding vessel is seen running into a smaller nodule anteromedially (arrow).

be complete resolution of nodules or residual scarring.

The differential diagnosis includes pulmonary emboli (thromboembolic or septic) fungal infection and haematogenous metastases.

Air space opacities—These were seen in 50% of cases in a review by Cordier *et al*¹⁵² and may be (1) bilateral, diffuse, or patchy areas of ground glass, which occasionally cleared spontaneously or (2) dense, localised consolidation with ill defined margins, with occasional cavitation.¹⁵² Diffuse, bilateral, low density opacities were seen in the six patients with proven alveolar haemorrhage. In children, diffuse interstitial or air space opacities are more common than nodules on chest radiography¹⁵⁶ and computed tomography¹⁵⁷ and are often secondary to alveolar haemorrhage.

Wegener's granulomatosis must be differentiated from Goodpasture's syndrome (both commonly involve lung and kidneys) in a patient presenting with acute alveolar haemorrhage. Wegener's granulomatosis is commonly ANCA positive, whereas antiglomerular basement membrane antibodies are present in Goodpasture's, and the latter disease is confined to the lungs and kidneys.

Tracheobronchial involvement—Tracheobronchial narrowing, presenting with stridor, is recognised but uncommon. Initially, there is florid inflammatory tissue within the lumen

with subsequent fibrotic strictures.¹⁵⁸ In tracheal involvement, spiral computed tomography demonstrates stricturing in the subglottic region in 90%, with circumferential mucosal thickening.¹⁵⁹ Vocal cords were involved in 30%. Mucosal irregularity and ulceration were seen in 50% and involvement of tracheal rings, with irregular calcification and deformity, were seen in 20%. Coronal reformatting is useful in determining the longitudinal extent of disease. The main bronchi may also be involved.^{159 160}

Unusual findings—These include atelectasis, exudative pleural effusions, spontaneous pneumothorax, hilar and mediastinal lymph nodes, and calcification within an area of consolidation.^{152 155 156 161}

Treatment—Treatment of the ANCA positive small vessel vasculitides, with immunosuppressives, commonly results in side effects (43%) and dose regimens attempt to mitigate these.¹⁶² Complications include pneumonia with opportunistic organisms, which may be fatal and must be differentiated from the pulmonary vasculitis.¹⁵² There is an 80% five year survival, but disease free remission is unusual. Mortality often occurs soon after presentation, with acute pulmonary haemorrhage or in elderly patients with renal failure.¹⁶²

Churg-Strauss syndrome

This pANCA associated vasculitis is distinguished from Wegener's granulomatosis by the presence of asthma and eosinophilia, with the vasculitis usually developing within three years of the onset of asthma.¹⁵³ Cardiac involvement (pericarditis, myocarditis, pericardial effusions) is relatively common, causing 50% of deaths.¹⁶³ Pulmonary involvement, which causes less than 10% of deaths, includes asthma, pleural effusions (which may be eosinophilic), eosinophilic infiltrations, and diffuse alveolar haemorrhage.¹⁶⁴

Radiological features

Chest radiography—These abnormalities are common, occurring in up to 72% of cases and include transient patchy air space opacities, multiple non-segmental consolidations, which may be nodular and rarely cavitate, and diffuse interstitial opacities (fig 6).¹⁶⁵⁻¹⁶⁷ Changes are often peripheral, with no zonal predominance. Pleural effusions occur in nearly one third of cases.¹⁶⁸ Diffuse miliary nodules and large nodules with cavitation are unusual.¹⁶⁵ The differential diagnosis of the chest radiograph appearance includes Loeffler syndrome, allergic bronchopulmonary aspergillosis (ABPA), Wegener's granulomatosis, and microscopic polyangiitis. However distinctions can usually be made with clinical and serological features or on computed tomography (for example, confirmation of bronchiectasis in ABPA).

Computed tomography—This demonstrates ground glass or air space consolidation in 59% (10 of 17 patients).¹⁶⁹ A predominantly peripheral distribution was seen in six and patchy non-zonal distribution in four. Other findings include bronchiole wall and interlobular septal thickening, pulmonary nodules, and enlargement of peripheral vessels.^{167 169} In one case,



Figure 6 A 40 year old man presenting with dyspnoea, asthma, and eosinophilia. The chest radiograph demonstrates predominantly peripheral diffuse alveolar opacities, confirmed to be eosinophilic infiltrates.

histological appearances correlated well, with thickening of vessels, lymphatics, and subpleural/interlobular connective tissues due to eosinophil-rich inflammatory infiltrates, which were also seen in the intra-alveolar spaces.¹⁶⁷

Microscopic polyangiitis

This shares many features with Wegener's granulomatosis but without granulomatous inflammation. It is strongly associated with ANCA, most often pANCA, which, together with negative hepatitis B serology help to differentiate it from (classic) polyarteritis nodosa.¹⁵³ Histology confirms a small vessel vasculitis. Renal involvement occurs in 90% and pulmonary involvement in 50%.¹⁵³ It is the commonest cause of the pulmonary renal syndrome.¹⁷⁰ Pulmonary capillaritis causing diffuse alveolar haemorrhage is the most life threatening complication.¹⁵³

Henoch-Schönlein purpura

This small vessel immune complex vasculitis, predominantly affecting children, may develop after upper respiratory tract infection. There is vascular deposition of IgA dominant immune complexes. Pulmonary involvement is unusual, seen in 0%–6.25%.^{171 172} Diffuse alveolar haemorrhage may occur secondary to a diffuse alveolitis/capillaritis, the chest radiograph demonstrating patchy multifocal consolidations or transient ill defined infiltrations; effusions also occur.^{171 173} The prognosis is good, with supportive care usually being sufficient. End stage renal failure develops in 5%.¹⁵³

Essential cryoglobulinaemia

In this immune complex disease, inflammation of venules, capillaries, and arterioles is caused by accumulation of cryoglobulins. Patients present with purpura, arthralgias, and nephritis and associated hepatitis C infection.¹⁵³ Pulmonary involvement is rarely reported: one series described chest radiography appearances of

mild to moderate interstitial fibrosis in 78%.¹⁷⁴ Adult respiratory distress syndrome has also been reported.¹⁷⁵

Behçet's disease

This clinical triad of oral and genital ulceration and uveitis is a multisystem vasculitis of unknown aetiology affecting vessels of all sizes.¹⁷⁶ It is more common in young men from eastern Mediterranean countries and Japan. Pathognomonic laboratory or histological tests are lacking.¹⁷⁷

Pulmonary involvement—This is estimated at 5%–10% of patients, usually presenting with haemoptysis.^{178 179} Thoracic involvement includes pulmonary thromboemboli and infarction, superior vena cava thrombosis, and pulmonary artery aneurysm.¹⁷⁶ Histologically, there is a vasculitis, resulting in arterial aneurysms and thrombosis.¹⁷⁶ Haemoptysis carries a poor prognosis, with a 30% mortality within two years.¹⁸⁰ Pulmonary hypertension and right heart failure may develop.

Radiological appearances

Chest radiography findings—Airspace consolidation, seen in 56% of patients with lung involvement, is due to haemorrhage or infarction.^{181 182} Subpleural nodular opacities, seen in 33%–83%, may represent infarcts and occasionally cavitate, may resolve spontaneously and rarely lead to rupture into the pleural space.^{178 181} Hilar prominence on the chest radiograph represents dilated arteries seen on computed tomography.^{179 181} Mediastinal widening, seen in 56% of patients, correlated with mediastinal oedema secondary to venous thrombosis on computed tomography.¹⁸¹ Pleural effusions (secondary to pulmonary infarction or chylous secondary to superior vena cava obstruction¹⁸³) were identified in 30%.¹⁸¹ Atelectasis and elevation of the hemidiaphragm may be due to infarction.¹⁷⁹

Computed tomography—Pulmonary artery aneurysms, mural thrombus, and calcification may be seen.^{181 184} Thrombosis of the superior vena cava, with extension into the right atrium, is associated with mediastinal oedema.¹⁸¹ HRCT demonstrates irregular enlargement and cut offs of peripheral vessels seen longitudinally or a stellate configuration transversely.¹⁷⁹ The differential diagnosis of the pulmonary artery aneurysms in Behçet's include giant cell arteritis, mycotic aneurysm, and malformations of the pulmonary vessels.

Pulmonary angiography—This may demonstrate aneurysms, occlusions, and thromboemboli. Angiography is hazardous with clinical deterioration in 50% and formation of aneurysms at the puncture site.¹⁸⁰

Hughes-Stovin syndrome—This variant of Behçet's disease is the association of multiple pulmonary aneurysms with deep venous thrombosis.¹⁸⁵ There is no oral or genital ulceration. The chest radiography appearances are indistinguishable from Behçet's.

MEDIUM AND LARGE VESSEL VASCULITIS

Pulmonary involvement is rare. Pulmonary artery thrombosis, stenosis, and post-stenotic

Box 10: Diseases associated with diffuse alveolar haemorrhage*With capillaritis*

- Goodpasture's syndrome.
- Wegener's granulomatosis.
- Microscopic polyangiitis.
- Churg-Strauss syndrome.
- Cryoglobulinaemia.
- Henoch-Schönlein purpura.
- Behçet's syndrome.
- Connective tissue diseases (for example, SLE).
- Drug induced vasculitis.

Without capillaritis

- Idiopathic pulmonary haemosiderosis.
- Bleeding disorders (for example, disseminated intravascular coagulopathy, anticoagulants, thrombocytopenia).
- Adult respiratory distress syndrome.
- Toxic inhalation, trauma.

dilatation have been reported in Takayasu's arteritis.^{186 187} Case reports in giant cell arteritis, include recurrent bilateral cavitating pulmonary nodules, which revealed giant cell granulomas histologically,¹⁸⁸ interstitial lung disease,¹⁸⁹ and pulmonary artery aneurysm.¹⁹⁰

DIFFUSE ALVEOLAR HAEMORRHAGE

Diffuse alveolar haemorrhage may occur due to a pulmonary capillaritis or in a wide variety of other diseases with no capillaritis (box 10). In pulmonary capillaritis, a necrotising vasculitis causes capillary wall necrosis, usually associated with immune complex deposition. This leads to haemorrhage into the alveoli, resulting in the clinical syndrome of diffuse alveolar haemorrhage, with haemoptysis, dyspnoea, and anaemia.

Goodpasture's syndrome originally referred to diffuse alveolar haemorrhage occurring with rapidly progressive glomerulonephritis. The term is now restricted to the presence of antiglomerular basement membrane antibodies, which are demonstrated histologically along glomerular and alveolar capillary walls.

Chest radiography—Appearances are the same regardless of the underlying cause of haemorrhage and may be normal but usually demonstrate diffuse bilateral alveolar opacities sometimes with more discrete, punctate acinar rosettes, often perihilar with sparing of the apices (fig 7).^{191 192} Ground glass consolidation may be seen on computed tomography.¹⁹³ Rapid change in distribution of opacities may be noted, with clearing in one area and further bleeds in another. When bleeding stops, relatively rapid clearing occurs. Recurrent bleeds may lead to thickening of the alveolar basement membrane, interstitial fibrosis and haemosiderosis, which can lead to pulmonary hypertension. The appearance is difficult to distinguish from other causes of diffuse air space opacification, such as pulmonary oedema, infective consolidation or alveolar proteinosis. Bronchoalveolar lavage may be required to confirm the presence of haemorrhage or haemosiderin-laden macrophages.



Figure 7 Female patient with a pANCA positive vasculitis and acute dyspnoea. There is bilateral patchy air space shadowing typical of haemorrhage and a small right pleural effusion.

Carbon monoxide uptake is markedly increased and is a sensitive test for diffuse alveolar haemorrhage.¹⁹⁴

* * *

C. Miscellaneous

LYSOSOMAL STORAGE DISEASES

Lysosomal storage diseases are rare inherited metabolic disorders, usually autosomal recessive and most prevalent in Ashkenazi Jews. Gaucher's disease is the commonest, in which a deficiency of glucocerebrosidase activity results in accumulation and deposition of glucosyl ceramide in the reticuloendothelial system. Pulmonary involvement, seen in type 1, leads to dyspnoea and recurrent infections, culminating in respiratory failure.¹⁹⁵ In Niemann-Pick disease, the enzyme defect is sphingomyelinase, with accumulation of sphingomyelin. Presentation is in infancy or childhood. Lung involvement is variable, depending on the subtype of the disease but may cause death in infancy.¹⁹⁶⁻¹⁹⁸ BAL demonstrates lipid laden foamy macrophages.¹⁹⁹ Diagnosis is confirmed either by bone, liver, or lung biopsy.

Radiological features

Chest radiography may demonstrate alveolar opacities, a reticulonodular pattern, or bronchial wall thickening. Miliary shadowing has been reported.²⁰⁰ HRCT findings include interlobular septal thickening, nodules, alveolar opacities and focal air trapping^{195 199 201} (fig 8). Infiltrative disease may lead to pulmonary hypertension.

PULMONARY AMYLOIDOSIS

Amyloid, an inert proteinaceous material, is deposited extracellularly in various organs. Pulmonary involvement may be localised or part of systemic amyloidosis. Primary systemic amyloidosis is rare but involves the lungs more commonly than in secondary disease (due to chronic infection or monoclonal gammopathy), in which pulmonary involvement is unusual.²⁰² Patients present with cough, dyspnoea, or haemoptysis with tracheobronchial involvement (box 11). Untreated disease may be stable or progress to respiratory failure.²⁰³

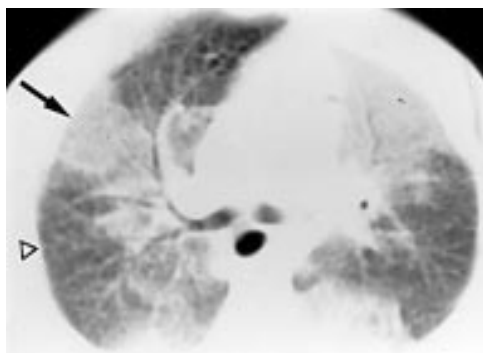


Figure 8 Computed tomography in a 4 year old girl with Gaucher's disease. Thickening of the interlobular septae (arrowhead) with ground glass opacity and air bronchograms (arrow) due to direct deposition of glucosyl ceramide.

The chest radiograph is usually normal²⁰⁴ with diffuse disease but may demonstrate a diffuse reticulonodular pattern, which may be associated with calcifications. There may be honeycombing.²⁰² The radiological appearances may mimic congestive cardiac failure, secondary to cardiac amyloid, the diagnosis being made at autopsy.²⁰³ Localised disease may involve the lung parenchyma or airways. Pulmonary nodules may be solitary or multiple, may cavitate and calcify. Airways involvement is usually indolent but may cause bronchial stenosis with distal atelectasis.²⁰³ Submucosal deposits may be multifocal, plaque-like, or polypoid. Lymphadenopathy may be massive and coarsely calcified.²⁰²

Pulmonary amyloid is rare. Sarcoidosis, granulomatous infections, neoplastic disease, and cardiac failure should be excluded.

PULMONARY LANGERHANS CELL HISTIOCYTOSIS

This uncommon disease of unknown aetiology usually presents in young adult smokers. There is diffuse involvement of the distal airways with granulomata, containing Langerhans cells, within the bronchial epithelium. The prognosis is variable, ranging from complete recovery to respiratory failure.²⁰⁵ Presentation is usually with symptoms of dry cough, chest pain, dyspnoea, or pneumothorax, although in some cases patients are asymptomatic, with changes noted on a chest radiograph.²⁰⁶

Box 11: Pulmonary manifestations of amyloid

Parenchymal

- Diffuse interstitial disease.*
- Nodules.*

Airways

- Submucosal deposits.
- Pseudotumour appearance.

Lymphadenopathy

Pleural

- Effusions.
- Thickening.

Cardiac

- Cardiomegaly.
- Pericardial effusion.

*Most common findings

Imaging features

The commonest chest radiography appearance is of bilateral symmetrical mid and upper zone micronodular or reticulonodular opacities, with sparing of the costophrenic angles. Larger nodules may mimic metastases. Multiple cystic air spaces and honeycombing may develop, with preservation or increase in lung volumes.^{207 208} On HRCT,²⁰⁷ the predominant finding is of cysts (17/18) and nodules (14/18), seen more sensitively than on chest radiography. The cysts are of varying sizes and shapes, may appear confluent, septate and although usually thin walled, may have a thick wall. Nodules vary widely in size but on average are about 5 mm. Cavitation may be present. Reticulation and ground glass is seen less frequently. The intervening lung is normal. Nodules may regress or evolve into cysts.²⁰⁹

The main differential diagnosis is lymphangiomyomatosis and these can be differentiated with reasonable accuracy on HRCT²: the presence of nodules, sparing of the costophrenic angles, and the presence of non-round cysts are features compatible with Langerhans cell histiocytosis.

ERDHEIM-CHESTER DISEASE

This rare disease is caused by an infiltration of mononuclear cells. Patients have lower limb osteosclerosis and 50% have extraskeletal manifestations. Lung involvement occurs in 20%–30% and causes significant mortality.²¹⁰ Chest radiography shows upper zone diffuse interstitial infiltrates, septal lines, and fissural thickening. Computed tomography demonstrates smooth thickening of pleura and interlobular septa, cystic areas, and ground glass opacities. Lung biopsy confirms the characteristic infiltrate of foamy histiocytes, with a striking lymphatic distribution and fibrosis.^{210 211}

PRIMARY CILIARY DYSKINESIA

There is abnormal structure and/or function of cilia with decreased motility in respiratory, auditory and spermatocyte cilia. This leads to bronchiectasis secondary to poor clearance of bronchial mucous. It may also result in situs inversus (Kartagener's syndrome), although this is not invariable.^{212 213}

Chest radiograph findings include bronchiectasis and hyperinflation.²¹² Computed tomography confirms bronchiectasis, diffuse centrilobular micronodules, and air trapping on expiratory films,²¹⁴ due to small airways plugging. The diagnosis is confirmed by electron microscopy and ciliary motility studies.²¹³

INFLAMMATORY BOWEL DISEASE

Pulmonary involvement is rare but well established, more commonly reported in ulcerative colitis than in Crohn's disease.²¹⁵ Pulmonary manifestations are diverse (box 12), however 50% are due to airways involvement, with chronic cough, which may be suppurative.^{215 216} Respiratory disease usually follows the onset of bowel disease but may rarely antedate bowel symptoms.

Box 12: Pulmonary manifestations of inflammatory bowel disease*Airways*

- Bronchiectasis.*
- Chronic bronchitis/suppuration.*
- BOOP.
- Subglottic stenosis.
- Chronic bronchiolitis.

Parenchymal

- Interstitial lung disease.*
- Pulmonary infiltrates with eosinophilia.
- Necrobiotic nodules (ulcerative colitis).

*Pleuritis*²¹⁵

*Most common findings



Figure 9 A 50 year old man with ulcerative colitis. HRCT demonstrates traction bronchiectasis secondary to fibrosing alveolitis (large arrow) and bronchiectasis (small arrow) with focal region of reduced attenuation and vascularity in the right lower lobe presumed secondary to small airways disease (arrowhead).

Chest radiography may demonstrate bronchial wall thickening or bronchiectasis. Computed tomography (fig 9) confirms bronchiectasis, signs of mucoid impaction, interstitial lung disease, or BOOP.^{215 216} Necrobiotic nodules mimic septic emboli or Wegener's nodules. Pleural fluid may occur with a serositis.²¹⁵

NEUROFIBROMATOSIS

Interstitial pulmonary fibrosis has been reported in 7%–20% of patients with neurofibromatosis, the pulmonary changes developing in adulthood.²¹⁷

Chest radiography characteristics are of diffuse linear interstitial densities and large bullae distributed predominantly in the upper lobes or apical segments of the lower lobes.^{218 219} HRCT confirms these appearances.²²⁰

Other non-pulmonary manifestations on the chest radiograph include neurofibromas, either intercostal, “dumbbell” (exiting the neural foramen) or in the overlying skin, intrathoracic meningoceles and changes in the ribs (ribbon ribs and rib notching due to the underlying mesenchymal defect and rib erosion by intercostal neurofibromas).

**TUBEROUS SCLEROSIS/
LYMPHANGIOLEIOMYOMATOSIS**

Tuberous sclerosis is a rare neuroectodermal disease with multiple hamartomas in a variety

of systems. Lung involvement occurs in 1% of cases. The clinical, histological, and radiological features of lung involvement are those of lymphangioleiomyomatosis, which is considered to be a forme fruste of tuberous sclerosis. Lymphangioleiomyomatosis is almost exclusively seen in women of reproductive age and is progressive, with a poor prognosis. Overgrowth of smooth muscle cells in the pulmonary lymphatics, blood vessels, and airways results in obstruction of the small airways with cyst formation and pneumothorax, chylothorax, and haemoptysis.

Radiological-clinical discrepancy may be seen at presentation, with severe airways limitation and a relatively normal chest radiograph. However, with disease progress, there is diffuse reticular shadowing bilaterally, with gradual hyperinflation and honeycombing. Recurrent spontaneous pneumothoraces and effusions are seen. On HRCT there is interlobular septal thickening, discrete cysts, which are uniformly distributed with no zonal predominance, and normal lung parenchyma between the cysts.^{221 222} Nodules are very rarely seen.²²¹ The differential diagnosis includes cryptogenic fibrosing alveolitis, emphysema, Langerhans cell histiocytosis, and a lymphangitic tumour.²

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