18.11.4 The lung in autoimmune rheumatic disorders

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18.11.4 The lung in autoimmune rheumatic disorders 4191 18.11.4 The lung in autoimmune rheumatic disorders M.A. Kokosi and A.U. Wells ESSENTIALS Lung complications occur in all rheumatological disorders, but their frequency and type vary strikingly between different systemic diseases. All components of the lungs can be affected, including the interstitium, airways, pleura, and pulmonary vasculature. Multicompartment involvement of the lung is characteristic. The distinction between subclinical involvement and clinically sig- nificant disease is a significant challenge with regard to treatment decisions. Particular autoimmune disorders Systemic sclerosis—pulmonary function is abnormal in up to 90% of cases. The most prevalent pattern of lung disease is nonspecific inter- stitial pneumonia. Both isolated pulmonary vascular disease and sec- ondary pulmonary hypertension occur. Lung cancer is increased in prevalence. Lung and pulmonary vascular disease are now the main cause of morbidity and mortality. Polymyositis/dermatomyositis—interstitial lung disease, usually with organizing pneumonia or nonspecific interstitial pneumonia, is the commonest pulmonary complication. Aspiration pneumonia is a frequent feature of advanced disease and a common cause of death. Rheumatoid arthritis—is associated with a wide range of pleuropulmonary complications, including interstitial lung dis- ease (with usual interstitial pneumonia the most frequent pattern, followed by nonspecific interstitial pneumonia), organizing pneu- monia, bronchiolitis obliterans, bronchiectasis, pleural

effusion, pul- monary vasculitis (rarely), and pulmonary rheumatoid nodules. Sjögren's syndrome—interstitial lung disease takes the form of fi- brotic nonspecific interstitial pneumonia or lymphocytic interstitial pneumonia. Tracheobronchial disease can be in the form of loss of mucus secretion in the trachea (xerotrachea), bronchi and bronchi- oles, or (less frequently) lymphocytic bronchiolitis. Systemic lupus erythematosus—clinically significant interstitial lung disease affects about 10% of patients, with nonspecific inter- stitial pneumonia the usual form. Acute lupus pneumonitis is an uncommon life-threatening disorder. Diffuse alveolar haemorrhage due to capillaritis can occur. The 'shrinking lung syndrome' is thought to be due to respiratory muscle weakness. Pulmonary hypertension is increasingly recognized. Pleural disease is common, affecting 50% of patients at some time. Pleuroparenchymal fibroelastosis—a newly recognized entity with dense intra-alveolar fibrosis and dense fibrous thickening of the vis- ceral pleura and adjacent lung, which has been described in rheum- atic disorders but its prevalence and clinical significance has yet to be defined. Management Is treatment required on account of lung disease?—it is critical that high-resolution CT findings and lung function tests are reconciled, with clear definition of all complications and deconstruction of the functional defect. Most clinicians regard DLco levels below 65% of predicted normal as indicative of clinically significant dis- ease. Maximal exercise testing is often useful in marginal cases. Careful monitoring with regular pulmonary function tests should be performed. Introduction of treatment for lung disease—the threshold for introducing therapy is reduced by three considerations: (1) the risk of progression of lung disease appears to be greatest early in the course of systemic disease; (2) severe functional impairment has consistently been associated with a higher mortality because it is indicative of a previously progressive course and an increased likeli- hood of future disease progression, also because loss of pulmonary reserve implies that the symptomatic consequences of a further pre- ventable loss of lung function may be substantial; and (3) observed disease progression is a major indication for treatment. Therapeutic options— immunomodulation remains the corner- stone of therapy. The intensity of the treatment depends on the disease phenotype and behaviour. Treatment decisions are less straightforward in rheumatoid arthritis-associated UIP. The place of antifibrotic drugs such as pirfenidone and nintedanib has yet to be established. Introduction Lung complications occur in all rheumatological disorders, but their frequency and type vary strikingly between different systemic diseases. Interstitial lung disease (ILD) and pulmonary vascular disease are now increasingly recognized, although the detection of limited abnormalities poses difficulties for clinicians who must now distinguish between subclinical involvement and clinically sig- nificant disease. The presence or absence of exertional dyspnoea is often misleading as musculoskeletal limitation may mask respira- tory symptoms or, alternatively, may cause exercise intolerance without lung pathology, due to the increased work associated with inefficient locomotion. Furthermore, ILD precedes the onset of sys- temic disease in some cases, although typical autoantibody profiles are often diagnostic. The range of lung histological patterns in rheumatological disease mirrors that seen in the idiopathic interstitial pneumonias, but pro- cesses are frequently admixed, with interstitial disease commonly associated with prominent lymphoid follicles (Fig. 18.11.4.1) or pleural thickening (Fig. 18.11.4.2). Nonspecific interstitial pneu- monia (NSIP), usual interstitial pneumonia (UIP), and organ- izing pneumonia are the most frequent findings, with lymphocytic interstitial pneumonia (LIP), acute interstitial pneumonia, and smoking-related disorders (desquamative interstitial pneumonia, respiratory bronchiolitis with associated interstitial lung disease) occurring in occasional cases. However, unlike the idiopathic inter- stitial pneumonias (see Chapters 18.11.1 and 18.11.2), NSIP is the most frequent pattern, especially in systemic sclerosis and polymyo- sitis/dermatomyositis, partly accounting for the better prognosis consistently reported in lung

involvement in rheumatological dis- orders compared to idiopathic disease in which UIP predominates. The outcome is usually better than in idiopathic fibrotic interstitial pneumonias. Of note, a UIP pattern in connective tissue disorders

section 18 Respiratory disorders 4192 has been suggested to have a better prognosis than idiopathic pul- monary fibrosis. Rheumatoid arthritis-associated UIP has had a worse prognosis than NSIP in recent series, but overall it seems that UIP does not have a uniformly poor outcome in rheumatoid arthritis. The clinical features of lung disease in particular rheumatological disorders will now be discussed, followed by consideration of key problems and treatments. Systemic sclerosis The diagnostic criteria for systemic sclerosis are detailed in Chapter 19.11.3. Pulmonary involvement (Tables 18.11.4.1 and 18.11.4.2), whether due to lung or pulmonary vascular disease, is now the major source of morbidity and mortality. Interstitial lung disease Lung disease (Table 18.11.4.2), which consists of NSIP in most cases (Fig. 18.11.4.3), occasionally precedes systemic symp- toms. Exertional dyspnoea (reported by over 50% of patients at some stage of disease) is the commonest presenting feature. Non- productive cough is less frequent and pleuritic chest pain is un- common. Digital clubbing is rare and should raise the suspicion of underlying malignancy. Fine, predominantly basal ‘Velcro’ crackles are present. Raynaud’s phenomenon is a useful clue to the underlying systemic diagnosis, which—in limited disease—is confirmed by capillaroscopy, digital thermography, strongly posi- tive antinuclear antibodies and, in most cases, the presence of the Scl 70 anti-DNA topoisomerase autoantibody. ILD is present on chest imaging at some stage in most patients and may be associ- ated with oesophageal dilatation. Lung function is abnormal in up to 90% of cases, but reduction in carbon monoxide diffusing capacity (DLco), the most frequent functional defect, does not in isolation discriminate between interstitial lung disease and pul- monary vasculopathy. Bronchoalveolar lavage is often performed to exclude underlying infection but does not have prognostic value. In NSIP and UIP, granulocytes and lymphocytes are often present in excess, whereas a lymphocytosis is the rule in organizing pneumonia, with a granulocytosis usually indicative of supervening fibrosis. Pulmonary vascular disease Both isolated pulmonary vascular disease and secondary pulmonary hypertension (complicating extensive interstitial lung disease) occur. Isolated pulmonary vascular disease takes the form of con- centric fibrosis, with ablation of arteriolar intima and media but no vasculitic element. This mainly complicates limited systemic scler- osis (including the CREST syndrome—calcinosis, Raynaud’s phe- nomenon, oesophageal dysmotility, sclerodactyly, teleangiectasia) and is typically associated with the anticentromere autoantibody. There is usually no evidence of interstitial lung disease on chest radi- ography, high-resolution CT, or bronchoalveolar lavage, and lung function tests generally show an isolated fall in DLco or a dispropor- tionate reduction in DLco in patients with coexisting lung involve- ment. Doppler echocardiography is often diagnostic and is widely used as a screening test, but is insensitive in early disease because of the large reserve in the pulmonary vascular bed. Isolated pulmonary vascular disease is a common cause of mortality and is partly re- sponsible for the very poor prognosis associated with marked reduc- tion in DLco in clinical series. Other pulmonary complications Lung cancer is increased in prevalence, even in nonsmokers, with adenocarcinoma more frequent than other histological subtypes. Extrapulmonic restriction due to severe cutaneous involvement is an Fig. 18.11.4.1 A case of rheumatoid arthritis involving the lung, with diffuse interstitial fibrosis (fibrotic nonspecific interstitial pneumonia) and prominent lymphoid follicles (reactive germinal centres): an association that is typical of rheumatoid lung. Fig. 18.11.4.2 A case of systemic lupus erythematosis showing thickening of the visceral pleura in association with fibrotic nonspecific interstitial pneumonia.

18.11.4 The lung in autoimmune rheumatic disorders 4193 extremely rare finding. Pleural disease and organizing pneumonia have been reported occasionally. Despite the fact that oesophageal dysfunction is common, aspiration pneumonia seldom occurs. Polymyositis/dermatomyositis Diagnostic criteria for polymyositis and dermatomyositis are de- scribed in Chapter 19.11.5. Pulmonary disease (Table 18.11.4.1), occurring in up to 60% of patients, is the most frequent cause of death. Pleural and airways involvement are rare. Interstitial lung disease Interstitial lung disease is the commonest pulmonary complication of polymyositis/dermatomyositis (Table 18.11.4.2). Although the presentation is usually with organizing pneumonia or NSIP, a rap- idly progressive form of acute pneumonitis occurs more frequently than in other rheumatological disorders. Lung disease (usually or- ganizing pneumonia) precedes systemic disease in up to one-third of patients. Acute exacerbation can occur and manifests as acute or subacute diffuse alveolar damage. Pulmonary capillaritis resulting in haemoptysis has occasionally been reported. Exertional dyspnoea is a common presenting symptom and orthopnoea is occasionally prominent, especially when myopathy is severe. Cough is a frequent feature, especially in organizing pneu- monia, but is seldom severe. Haemoptysis and pleuritic chest pain are rare. In fibrotic disease, fine basal 'Velcro' crackles are usual, and these are variably present in organizing pneumonia. Organizing pneumonia is often obvious on chest radiography, but high-resolution CT is usually diagnostic and demonstrates the characteristic combination of patchy consolidation and fi- brotic disease with bronchocentric and lower zone distribution (the classic form of admixed NSIP and organizing pneumonia). Lung function tests usually show a restrictive ventilatory defect with a reduction in DLco. When reduced lung volumes are associ- ated with preservation of DLco and an increase in the gas transfer index (Kco), extrapulmonic restriction due to respiratory muscle weakness should be suspected. Bronchoalveolar lavage is useful in discriminating between infection and autoimmune organiz ing pneumonia, especially when immunosuppressive therapy has previously been instituted for systemic disease, but has little value in prognostic evaluation. Autoantibodies to aminoacyl-tRNA synthetase, especially Jo-1 (antihistidyl tRNA synthetase) are often present when prominent inflammatory myopathy coexists with dif- fuse lung disease, but are found in less than 5% of patients without diffuse lung disease. Other pulmonary manifestations Aspiration pneumonia, a very frequent feature of advanced disease and a common cause of death, should also be considered in earlier disease if there is upper airway/pharyngeal or oesophageal muscle weakness, especially when the dependent lung regions are select- ively involved. Respiratory muscle weakness, occurring in up to 5% of patients, may occasionally lead to hypercapnic respiratory failure but requires muscle function testing for confirmation in milder cases. Mild pulmonary hypertension is increasingly recognized, al- though the exact prevalence is uncertain, but vascular involvement is generally self-limited. Lung cancer has increased incidence in polymyositis/dermatomyositis, which in these cases might represent a paraneoplastic feature.

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

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

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

Lung pattern	Rheumatoid arthritis	Systemic sclerosis	Polymyositis/ dermatomyositis	Systemic lupus erythematosus	Sjögren's syndrome
Usual interstitial pneumonia	++	+	+	+	±

Nonspecific interstitial pneumonia ++ +++ ++ ++ ++ Organizing pneumonia + ± ++ ± ± Lymphocytic interstitial pneumonia ± ± ± ± ++ Pleuroparenchymal fibroelastosis ? ? ? ? ? Desquamative interstitial pneumonia and/or RB-ILD ± ± ± ± ± Diffuse alveolar damage + ± + + ±

section 18 Respiratory disorders 4194 Rheumatoid arthritis Diagnostic criteria for rheumatoid arthritis are detailed in Chapter 19.5. Pleuropulmonary complications (Table 18.11.4.1) are more variable than in other rheumatological disorders. Interstitial lung disease Interstitial lung disease (Table 18.11.4.2) has a male predominance (male:female 3:1) and is associated with high titres of rheumatoid factor, the presence of rheumatoid nodules, a history of smoking, and HLA B8 and HLA Dw3 positivity. UIP is the most preva- lent histologic pattern in rheumatoid arthritis, followed by NSIP. Interstitial lung disease precedes the onset of systemic disease in about 15% of cases. Exertional dyspnoea is the most frequent presenting symptom, with nonproductive cough also common, especially in patients with sicca symptoms. Bilateral, predominantly basal 'Velcro' crackles are usual and digital clubbing is more prevalent than in other rheum- atological diseases. Acute exacerbations of underlying interstitial lung disease can occur and have poor prognosis, similar to that of acute exacerba- tions in idiopathic pulmonary fibrosis. Drug reactions and infec- tions should be considered in the case of acute deterioration. Radiologically overt interstitial lung disease, usually with a basal predominance, was present in less than 5% of cases in three large chest radiographic series. High-resolution CT often shows limited interstitial abnormalities when chest radiographs are normal, al- though the significance of 'subclinical' disease has yet to be as- certained. In established disease, a restrictive ventilatory defect is associated with reduced DLco levels, but an isolated reduction of DLco is seen in up to 40% of unselected rheumatoid arthritis patients. As in other rheumatological disorders, bronchoalveolar lavage may be very useful when opportunistic infection is sus- pected, but it has limited routine value when disease is overtly fibrotic. Organizing pneumonia Organizing pneumonia more commonly mimics infectious pneu- monia in rheumatoid arthritis than in polymyositis/dermatomyo- sitis. Cough and exertional dyspnoea are commonly accompanied by fever and weight loss. There is multifocal consolidation on chest radiography and high-resolution CT. Lung function tests show a restrictive defect and reduced DLco, often associated with disproportionate hypoxia due to shunting through consolidated lung. A lymphocytosis is usual on bronchoalveolar lavage, with a granulocytosis usually indicative of underlying fibrotic disease. Organizing pneumonia responds well to corticosteroid therapy in most cases. Bronchiolitis obliterans This rare but often lethal bronchiolar disorder usually presents with exertional dyspnoea, often with a component of wheeze and non- productive cough. The breath sounds are usually quiet, with inspira- tory 'squawks' a very specific sign of small-airways disease. An association with the use of penicillamine was postulated in the first descriptions of obliterative bronchiolitis 20 to 30 years ago. Based on subsequent case reports and small series this is probably a true association, but it should be stressed that more cases of oblit- erative bronchiolitis are seen in patients with rheumatoid arthritis who have not used penicillamine than in those who have. The chest radiograph is normal or shows hyperinflation. High- resolution CT shows a 'mosaic' pattern which is more obvious on expiratory images and represents regional gas trapping. In most cases the lung function defect is obstructive, although there is oc- casionally a mixed obstructive/restrictive pattern. Measures of gas transfer (DLco and Kco) are preserved provided the forced ex- piratory volume in 1 s (FEV1) exceeds 1 litre. Preservation of gas transfer is especially useful in discriminating between oblitera- tive bronchiolitis and emphysema, in which both DLco and Kco are significantly reduced. Bronchiolitis obliterans is characterized histologically by fibrous destruction and ablation of the terminal bronchiolar wall by

granulation tissue. Although a fatal outcome was almost invariable in early reports, the increasing use of high-resolution CT has disclosed many pa- tients with milder disease in whom the course is often indolent. Bronchiectasis Bronchiectasis is more prevalent in rheumatoid arthritis than in other rheumatological diseases. From a definitive literature re- view of 289 rheumatoid arthritis patients with associated bron- chiectasis reported since 1928, it is clear that the condition precedes the onset of systemic disease in some cases. Before the routine use of high-resolution CT bronchiectasis was generally diagnosed in patients presenting with chronic purulent sputum production. However, it is increasingly apparent that asymptom- atic (‘dry’) bronchiectasis is extremely common, being present on high-resolution CT in 30% of 50 rheumatoid arthritis patients with normal chest radiographs on prospective evaluation. The high-resolution CT overlap between bronchiectasis and oblitera- tive bronchiolitis should be stressed. Bronchiectasis and a ‘mo- saic’ pattern may coexist in both disorders, and bronchiectasis is often present in rheumatoid arthritis patients with interstitial lung disease. Fig. 18.11.4.3 High-resolution CT scan in a patient with systemic sclerosis. There is prominent ground-glass attenuation, admixed with fine reticular abnormalities: these appearances are typical of nonspecific interstitial pneumonia.

18.11.4 The lung in autoimmune rheumatic disorders 4195 Pleural disease Pleural involvement is present at autopsy in about 50% of cases, but only 20% of patients experience pleuritic pain at some stage and most pleural effusions are found incidentally on chest radiography. Clinically overt pleural effusions occur in less than 5% of patients, usually in males, but evidence of pre-existing pleural disease is found on screening chest radiography in up to 20%. Pleural disease has been linked to the presence of rheumatoid nodules but not to more severe systemic disease. Symptoms are confined to a minority of cases and generally con- sist of pleuritic pain and prominent fever, often necessitating the ex- clusion of empyema. Effusions may occasionally develop acutely in association with pericarditis or exacerbations of arthritis. Dyspnoea may result from pulmonary compression when effusions are large, especially when there is underlying interstitial lung disease. The fluid is exudative, with a low glucose level, a low pH, and usually a predominant lymphocytosis. The most frequent histological finding is replacement of the normal mesothelial cell covering by a pseudostratified layer of epithelioid cells, with focal multinucleated giant cells and regular small papillae containing branching capil- laries, but no necrosis or granulomata. These findings are pathog- nomonic for rheumatoid pleuritis when present, but histological appearances are often nonspecific. Some cases respond well to corticosteroid therapy, but more often remission is at best partial. Pulmonary vasculitis Pulmonary vasculitis is a surprisingly uncommon complication of rheumatoid arthritis given the relatively high prevalence of systemic vasculitis in the disease. However, it is likely that pulmonary vas- culitis is not detected in many cases as the diagnosis is often elu- sive. Diffuse alveolar haemorrhage has been reported in a handful of cases. Pulmonary rheumatoid nodules These are present on chest radiography in less than 1% of patients and are usually associated with subcutaneous rheumatoid nodules. Caplan’s syndrome consists of the association of pulmonary nodules, especially cavitating nodules, with coal miner’s pneumoconiosis. Single nodules in cigarette smokers often require histological con- firmation of the diagnosis (by means of percutaneous needle or surgical biopsy) as malignancy cannot be excluded noninvasively. Nodules may fluctuate in size, waxing and waning with variations in underlying rheumatoid activity, and can reach 5–10 cm in diam- eter. Usually nodules are asymptomatic and found incidentally on chest radiography, but they often cavitate (50%) and can rupture, giving rise to haemoptysis, pneumothorax, or bronchopleural fis- tula. Multiple nodules occasionally occur, with respiratory failure a reported complication of intense nodular infiltration. Other pulmonary

manifestations Nonproductive cough due to secondary Sjögren's syndrome is not uncommon in rheumatoid arthritis and may result from either im- paction of viscid secretions within small airways or from a lympho- cytic bronchiolitis, often associated with enlargement of lymphoid follicles. Full-blown follicular bronchiolitis is a rare disorder (see Chapter 18.11.3), in which reticulonodular chest radiographic appearances are often suggestive of interstitial lung disease and lung function tests may be restrictive or obstructive. Unlike obliterative bronchiolitis, follicular bronchiolitis often responds to cortico- steroid therapy. Lymphocytic interstitial pneumonia is a rare benign lymphoproliferative disorder which may be limited or extensive, presents as an interstitial lung disease, and is variably responsive to corticosteroids. Desquamative interstitial pneumonia is rare. Lower respiratory tract infection is increased in fre- quency in rheumatoid arthritis, especially in advanced disease. Bronchopneumonia is a common terminal event, accounting for 15 to 20% of deaths. Pulmonary hypertension occurs in up to 20% of patients with rheumatoid arthritis and is usually mild and secondary to inter- stitial lung disease, but occasionally it can result from a primary vasculopathy. Sjögren's syndrome The diagnostic criteria for Sjögren's syndrome are detailed in Chapter 19.11.4. There is evidence of pulmonary abnormalities (Table 18.11.4.1) in about one-quarter of cases, but disease is usu- ally self-limited and seldom progresses to severe disability or death. Interstitial lung disease Parenchymal disease (Table 18.11.4.2), once thought to consist ex- clusively of lymphocytic infiltration (lymphocytic interstitial pneu- monia) based on historical series, occurs in up to 10% of patients. However, it is increasingly recognized that clinically significant disease more often consists of fibrotic NSIP (with UIP very seldom reported). Interstitial lung disease is often asymptomatic but may declare it- self with cough or exertional dyspnoea. The findings are nonspecific, consisting of crackles on auscultation, reticular or reticulonodular abnormalities on chest radiography, and a restrictive ventilatory defect associated with a reduction in DLco. High-resolution CT discriminates usefully between these processes. Fibrotic NSIP is characterized by reticular abnormalities and traction bronchiectasis and in some occasions ground glass. LIP is characterized by ground glass and cystic changes. LIP can evolve to pulmonary lymphoma occasionally. Extrapulmonary lymphoma is also increased in preva- lence in Sjögren's syndrome and is probably as frequent as pulmonary lymphoma. Lymphoma often mimics organizing pneumonia, which has occasionally been reported in Sjögren's syndrome. Tracheobronchial disease Tracheobronchial disease may take two forms. The more fre- quent disorder consists of loss of mucus secretion in the trachea (xerotrachea), bronchi, and bronchioles. Xerotrachea occurs in up to 25% of patients with primary Sjögren's syndrome in older series, but may be less prevalent with the increasing recognition of milder variants of the syndrome. The histological picture con- sists of atrophy of tracheobronchial mucous glands, with or without a lymphoplasmacytic infiltrate. Less frequently, airway disease is due to a lymphocytic bronchiolitis, and occasionally there is con- siderable enlargement of lymphoid follicles (follicular bronchio- litis). Both xerotrachea and lymphocytic bronchiolitis present with an unremitting dry cough. Endobronchial inflammation is often

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

Xerotrachea responds variably to nebulized saline. Systemic lupus erythematosus The diagnostic criteria for systemic lupus erythematosus (SLE) are detailed in Chapter 19.11.2. Pleuropulmonary manifestations are listed in Table 18.11.4.1. Diffuse lung disease Although limited interstitial fibrosis is found at autopsy in up to 70% of patients, it is likely that this represents post-inflammatory sequelae in most cases. Clinically significant interstitial lung dis- ease is present in less than 5% of patients at the onset of systemic disease, and develops in a further 5% during follow-up. The clin- ical presentation closely resembles that of interstitial lung disease in other rheumatological disorders and typically includes dyspnoea, cough, predominantly basal crackles and a restrictive lung func- tion defect or isolated reduction in DLco, and predominantly basal reticulonodular abnormalities on chest radiography. There are no definitive reports of typical high-resolution CT appearances, al- though there is a high prevalence of limited subclinical interstitial abnormalities. The most common histological pattern is NSIP, al- though UIP has also been reported (Fig. 18.11.4.2). Acute lupus pneumonitis is an uncommon life-threatening dis- order, seen in less than 2% of patients, but with a mortality rate des- pite treatment of up to 50% once respiratory failure has developed. It may resemble organizing pneumonia, which is very infrequent in SLE. It is believed by some that acute lupus pneumonitis represents an aberrant immunological response to infection, facilitated by the intrinsic immune defect of the systemic disease. Extrapulmonary restriction Extrapulmonary restriction in SLE takes the form of the ‘shrinking lung syndrome’, consisting of a marked reduction in lung volume on chest radiography in association with a restrictive functional de- fect, preservation of DLco, and a marked increase in Kco. The lung interstitium is normal and the disorder is thought to represent re- spiratory muscle weakness, especially diaphragmatic weakness. The syndrome is usually self-limited, although producing severe exer- cise limitation in more advanced cases. Improvements have been reported with corticosteroid or immunosuppressive therapy, but these appear to be unpredictable and there is no other efficacious treatment. Diffuse alveolar haemorrhage Diffuse alveolar haemorrhage due to capillaritis occurs more fre- quently than in other rheumatological conditions but is still rare in SLE. It occurs in 1.5% of cases, and is the initial presenta- tion in 10–20% of these. Typically, patients present with subacute or acute dyspnoea and extensive infiltrates on chest radiography. Haemoptysis is occasionally torrential but is more often minimal or absent, even when there is extensive intra-alveolar haemorrhage. The presentation is similar to those of acute lupus pneumonitis and opportunistic infection, especially in the absence of haemoptysis. The diagnosis is best made by bronchoalveolar lavage, when in- creasingly heavy blood-staining is typical as the distal airways are lavaged in cases without overt endobronchial haemorrhage. Diffuse alveolar haemorrhage is life-threatening with a mortality of up to 50% in patients with respiratory failure. There are no definitive treat- ment data, but empirical treatments have included intravenous cor-ticosteroid therapy, intravenous cyclophosphamide, rituximab, and plasmapheresis. Pulmonary hypertension Pulmonary hypertension, once regarded as rare, is encountered with increasing frequency. In early reports, largely containing pa- tients with severe disease, the 2-year mortality approached 50%. However, with the increasing use of echocardiography, subclin- ical pulmonary vascular abnormalities are detected in 10% of pa- tients. In some cases associated with Raynaud’s phenomenon it appears that vasoconstriction with secondary irreversible damage is the dominant pathophysiological mechanism. In other cases vasculitis predominates, and this may respond strikingly to cor- ticosteroid therapy or intravenous cyclophosphamide, even in ad- vanced disease. Thromboembolism or microthrombosis in small intrapulmonary arterioles also occur in many cases, especially when antiphospholipid antibodies are present. It is often impossible to determine which mechanism predominates as surgical biopsy is contraindicated by severe pulmonary hypertension.

Treatment is empirical, consisting of immunosuppression, anticoagulation, and a variety of vasodilator agents. Pleural disease Pleural disease is common in SLE. There is clinical or radiographic evidence of pleural involvement in 20% of patients at the onset of systemic disease, and at least 50% have overt pleural involvement at some time. Pleural disease is often detected on incidental chest radiography in asymptomatic patients, but in other cases pleur- itic pain is recurrent or intractable. The pleural fluid is usually serosanguinous and exudative, with a high neutrophil content in patients with pleurisy, but a predominant lymphocytosis is the rule in chronic disease and in some cases, effusions are haemorrhagic. Corticosteroid therapy is usually much more efficacious than in rheumatoid arthritis. Relapsing polychondritis Relapsing polychondritis is described in Chapter 19.11.9. Respiratory involvement accounts for about 10% of deaths and takes the form of obstruction of the glottis, trachea, and bronchi, leading to airway stricture, collapse, and distal infection. Pulmonary vas- culitis is common but often subclinical, and pulmonary hyperten- sion is rare. Parenchymal disease seldom occurs in isolated relapsing polychondritis, but many other autoimmune conditions, including

18.11.4 The lung in autoimmune rheumatic disorders 4197 most rheumatological disorders, are associated with relapsing polychondritis and may be complicated by interstitial lung disease. Lung function tests typically show severe airflow obstruction due to airway collapse, with reduced maximal inspiratory and expiratory flow representing extrathoracic and intrathoracic airway involve- ment, respectively. Airway abnormalities are prominent on chest radiography, with bronchiectasis and bronchial wall thickening evident on high-resolution CT. Bronchoscopy has been reported to trigger fatal airway obstruction and should be undertaken with caution. The diagnosis may be made using dynamic CT scanning showing collapse of the larger airways on inspiratory manoeuvres. However, definitive diagnosis requires biopsy, which often shows characteristic features in extrapulmonary cartilaginous areas. Immunosuppression is sometimes effective in preventing disease progression, and mechanical stenting may be life-saving in advanced destructive disease. Traditionally, flares of relapsing polychondritis have been treated with corticosteroid therapy or immunosuppres- sants, but—based on recent accumulated experience—anti-TNF agents are increasingly used, and they are advocated by some as first- line treatment. Ankylosing spondylitis Ankylosing spondylitis is described in Chapter 19.6. Interstitial lung disease is a rare complication, identified on chest radiography in less than 2% of cases, although subclinical interstitial abnormal- ities are highly prevalent on high-resolution CT, including fibrotic abnormalities and paraseptal emphysema. Fibrobullous lung dis- ease is largely or entirely confined to the upper zones and is usually symmetrical. Fibrotic abnormalities may be more extensive in occa- sional patients with severe long-standing spinal disease. Interstitial lung disease does not respond to corticosteroid therapy and immunosuppressive therapy has no recognized role and may predispose to chronic infection. Cavities tend to develop within distorted fibrotic apical tissue and are often colonized by myco- bacteria or fungi, especially Aspergillus fumigatus. Life-threatening haemoptysis is an occasional complication of intracavitary myce- toma formation. Bronchial artery embolization is sometimes ef- fective, but surgical resection of a mycetoma is generally held to be contraindicated and carries a high mortality due to postoperative bronchopleural fistula formation and empyema. Extrapulmonary restriction is more frequent than interstitial lung disease and results from immobilization of the chest wall due to fu- sion of the costovertebral joints. This complication is often asymp- tomatic and the lung function defect is mild, perhaps because the diaphragm is able to compensate for chest-wall immobility. Exercise tolerance is seldom impaired, provided that an active lifestyle is maintained. Chest-wall fixation

increases in prevalence and severity in long-standing disease and does not respond to anti-inflammatory treatment. Management is confined to spinal extension exercises and the maintenance of general fitness with exercise programmes. Mixed connective tissue disease In this syndrome there are variable features of SLE, systemic scler- osis, and polymyositis/dermatomyositis in association with high titres of autoantibody directed against the extractable nuclear antigen U1-RNP. However, the diagnosis is often elusive because clinical features evolve as disease progresses and individual criteria may be ephemeral. Pulmonary involvement encompasses the full spectrum of disease seen in systemic sclerosis, polymyositis/dermatomyositis, and SLE, the three most frequent disorders being pleural effusions, interstitial lung disease, and pulmonary hypertension. Pleuritic pain is reported by up to 40% of patients, but effusions are typically small and generally remit spontaneously. Interstitial lung disease is even more prevalent and usually mimics the inter- stitial fibrosis of systemic sclerosis: organizing pneumonia is sur- prisingly infrequent and, when present, is generally self-limited. Pulmonary vascular disease is well recognized and is occasion- ally fatal: reported mechanisms include, most commonly, vaso- constriction in association with arteriolar obliteration, as in systemic sclerosis, but also pulmonary vasculitis and pulmonary thromboembolism. Other rare pulmonary complications are those of the dominant rheumatological picture and include respiratory muscle weakness, severe diffuse alveolar haemorrhage, aspiration pneumonia due to pharyngeal dysfunction, and opportunistic infection in patients receiving immunosuppressive therapy. The investigation and man- agement of pulmonary complications is as for the individual rheum- atological diseases. Long-term outcome has not been quantified with any precision. Undifferentiated connective tissue disease Many patients with an idiopathic interstitial pneumonia have clin- ical features that suggest an underlying autoimmune process but do not meet established criteria for a connective tissue disease. Researchers have proposed differing criteria and terms to describe these patients, and lack of consensus recently led to the proposal of interstitial pneumonitis with autoimmune features (IPAF). The clas- sification criteria are organized around the presence of a combin- ation of features from three domains: a clinical domain consisting of specific extrathoracic features, a serologic domain consisting of specific autoantibodies, and a morphologic domain consisting of specific chest imaging, histopathologic, or pulmonary physiologic features. The definition of IPAF requires that the patient fulfils two of the three domains. The clinical significance of IPAF needs to be further studied. Key clinical problems in interstitial lung disease in patients with rheumatological disorders Detection of disease The reported prevalence of interstitial lung disease is critically de- pendent on which diagnostic modality is used. Rheumatoid arthritis patients without overt lung involvement were found to have inter- stitial fibrosis in almost one-half of cases in an early biopsy study, yet abnormalities are present on chest radiography in less than 5%. Chest radiography is now known to be insensitive and symptoms are often misleading. There is an increasing tendency to screen patients with rheuma- toid arthritis, systemic sclerosis, and polymyositis/dermatomyositis

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

disease, pleural disease, respiratory muscle weakness, and other forms of extrapulmonary limitation. Bronchoalveolar lavage was once widely advocated as a means of detecting underlying alveolitis, but abnormalities are present in most patients with systemic sclerosis, ankylosing spondyl- itis, and Sjögren's syndrome, and are probably equally prevalent in the other rheumatological diseases. Subclinical alveolitis has never been shown to evolve into clinically significant intersti- tial lung disease and hence this use of bronchoalveolar lavage is largely discredited. High-resolution CT is the most sensi- tive and reliable means of detecting interstitial lung disease but should probably be reserved for patients with symptoms, chest radiographic abnormalities, lung function impairment, or high- risk patients (e.g. patients with systematic sclerosis (SSc) who are positive for anti-topoisomerase or anti-RNA polymerase III antibodies). Determination of clinically significant disease The advent of high-resolution CT has undoubtedly helped clin- icians greatly in identifying interstitial lung disease, but has led to a separate problem: the identification of limited subclinical abnormalities. Severe interstitial fibrosis is rare in Sjögren's syn- drome, SLE, and ankylosing spondylitis, but high-resolution CT abnormalities are present in many patients. In unselected patients with rheumatoid arthritis, interstitial lung disease is evident in 25% of cases, but clinically overt pulmonary fibrosis develops in less than 10%. It is inappropriate to base treatment decisions on high-resolution CT findings in isolation, but the interpretation of lung function tests is often complicated by the coexistence of interstitial lung disease and other processes, especially pul- monary vascular disease and pleural disease. High-resolution CT findings and lung function tests must be rec- onciled, with a clear definition of all complications and deconstruc- tion of the functional defect. In this way, the degree of functional impairment ascribable to parenchymal lung disease can usually be approximately apportioned. Except in patients with a severe restrictive ventilatory defect, DLco levels provide the best overall guide to disease severity. Although there is no exact consensus, most clinicians regard DLco levels below 65% of predicted normal as indicative of clinically significant disease. In marginal cases, max- imal exercise testing is often useful, as respiratory symptoms may be shown to result from musculoskeletal limitation (i.e. there is no desaturation or widening of the alveolar–arterial oxygen gradient at the limits of exercise). However, there is lingering doubt as to whether abnormalities are clinically significant in many cases and in this situation, there is no substitute for careful monitoring, with regular repetition of pulmonary function tests if treatment is not in- stituted immediately. Prognostic evaluation and when to treat The decision as to whether to start treatment is often a very close call. Many patients have intrinsically stable disease and hence the introduction of immunosuppressive therapy in attempt to prevent disease progression is often unnecessary and may result in avoidable drug toxicity. Accurate prognostic evaluation is essential, with treatment ideally reserved for patients at higher risk of progression, but this goal is not straightforward. It is important that the few patients with predom- inantly inflammatory disease be identified, with a view to therapy aimed at reversing disease and restoring lung function. High- resolution CT plays a significant role in this regard: patients with organizing pneumonia and other forms of inflammatory cell infil- tration are readily identifiable from characteristic high-resolution CT patterns. However, most patients have underlying irreversible interstitial fibrosis, most commonly taking the form of fibrotic NSIP. The pattern of disease at surgical biopsy can be an invaluable aide to management in the idiopathic interstitial pneumonias, but has little to offer in this respect in the rheumatological disorders, in which the distinction between NSIP and UIP seems to be less important (except, possibly, in rheumatoid arthritis). The morphological defin- ition of interstitial fibrosis using high-resolution CT has yet to lead to reliable therapeutic recommendations. The presence of a bronchoalveolar lavage neutrophilia in sys- temic sclerosis was viewed as prognostically important

in patients with SSc-ILD. However, data from two large patient cohorts failed to confirm links between disease progression and neutrophilia of the bronchoalveolar lavage (BAL) fluid. Similarly, despite the fact that the prevalence of SSc-ILD is much higher in SSc subgroups positive for anti-topoisomerase antibody and anti-RNA polymerase III anti- body, there is no evidence that progression of ILD differs materially according to autoantibody status. Biomarkers can be promising prognostic tools, but for the mo- ment no biomarker has been shown to reliably identify an increased risk of progression in CTD-ILD in a prospective study. Serum levels of KL-6 (a glycoprotein marker of lung epithelial cell turnover) cor- relate with the extent of systemic sclerosis-ILD and are higher in patients with active lung disease than in the remaining patients, but the prognostic value of KL-6 levels has yet to be quantified. A staging system based on assessment of disease severity has been proposed for the identification of systemic sclerosis-ILD associated with a poorer outcome. Patients with significantly worse survival can be identified by the rapid semi-quantitative assessment of extent of disease on CT, integrated with forced vital capacity (FVC) levels. Given the aforementioned, treatment must be based on general principles. The threshold for introducing therapy is reduced by the following three considerations: • The risk of progression of lung disease appears to be greatest early in the course of systemic disease. In systemic sclerosis this has long been recognized, with the risk of deterioration being highest in the first 4 years. In polymyositis/dermatomyositis acute life- threatening progression of disease is much more prevalent in the first year, especially when lung disease precedes systemic disease. The same principle applies to other rheumatological disorders, although there is a paucity of data. • Severe functional impairment has consistently been associated with a higher mortality in clinical series of rheumatological

 disorders. This is best documented in systemic sclerosis, with se- vere reduction in DLco and severe lung restriction both being ma-lignant prognostic determinants. The severity of disease becomes an increasingly important therapeutic consideration as DLco levels fall below 60% of predicted normal values. Severe disease requires treatment for two reasons. (1) it is indicative of a previ- ously progressive course and an increased likelihood of future dis- ease progression. (2) Loss of pulmonary reserve implies that the symptomatic consequences of a further preventable loss of lung function may be substantial. • Observed disease progression is a major indication for treatment, even when the systemic disease is long-standing and the func- tional defect is mild to moderate. In systemic sclerosis, decline in gas transfer over 1 to 3 years is associated with a substantially increase in mortality, although it is sometimes necessary to con- firm progression of lung disease (as opposed to worsening of pulmonary vascular disease) using serial high-resolution CT scanning. This is especially the case when the reduction in gas transfer is disproportionate. In view of the absence of a definitive evidence base, management strategies can usefully be built around the recently proposed ‘disease behaviour classification’, developed initially for the management of unclassifiable disease (Table 18.11.4.3). More specifically, treatment decisions are informed by the designation of disease into one of five categories, based on severity, cause (if present), the predominance of reversible or irreversible disease (as judged by high-resolution CT or biopsy appearances), and the combination of this information with the observed disease behaviour. Treatment The treatment of interstitial lung disease in rheumatological dis- orders has until recently been largely empirical, consisting of trad- itional immunomodulation, with corticosteroid monotherapy often used in mild disease and combination therapy with low-dose corticosteroids and immunosuppressive agents (such as cyclophos- phamide, azathioprine, methotrexate and mycophenolate mofetil) in more severe or progressive disease. When inflammatory dis- ease predominates, as in organizing pneumonia or

lymphocytic interstitial pneumonia, it is appropriate to treat for a therapeutic response with high-dose steroid therapy, or intense immunosup- pressive therapy in refractory cases. Following a response it has been usual to gradually reduce treatment to establish the minimum dose required to prevent relapse, and in many patients with organ- izing pneumonia it is eventually possible to withdraw treatment al- together, although continuation of careful monitoring is advisable in the long term. There is now ample evidence from several clinical series that this approach works well in most patients with polymyositis/ dermatomyositis, with corticosteroid monotherapy often highly efficacious, although it should be stressed that high-dose cortico- steroid therapy is associated with a greatly increased risk of renal crisis in systemic sclerosis and is strongly contraindicated in that disease. Treatment decisions are less straightforward in predominantly fibrotic disease. There is lack of controlled data on treatment of these disorders, with the only current placebo-controlled trials conducted in lung disease associated with systemic sclerosis. A placebo-controlled trial of oral cyclophosphamide therapy has shown a definite treatment effect, although the inclusion of many patients with mild disease makes it difficult to draw conclusions on its clinical significance. Intravenous cyclophosphamide, given at monthly intervals, is less toxic and may be equally efficacious, based on the amplitude of the treatment effect in a placebo-con- trolled evaluation (although the study was underpowered). In both studies the greater part of the effect was prevention of dis- ease progression, with regression of disease relatively infrequent. A Cochrane systematic review published in 2018 concluded that ‘small benefit may be derived from the use of cyclophosphamide’. The same broad principles are applicable in rheumatological disorders other than polymyositis/dermatomyositis and systemic sclerosis, but data remain sparse. The exception is rheumatoid arthritis-associated ILD, which is less responsive to immunosup- pression. The prominent UIP pattern in this entity raises the pos- sibility of the use of antifibrotic drugs (pirfenidone, nintedanib), as is the case in idiopathic pulmonary fibrosis, but this potential needs to be tested in clinical trials. In a large recent retrospective series of patients with CTD-ILD, mycophenolate mofetil therapy was associated with stabilization of disease for at least 2 years in most cases. More recently a ran- domized control trial of cyclophosphamide versus mycophenolate mofetil in systemic sclerosis associated ILD, showed similar effi- cacy of the two drugs on FVC, but a greater treatment effect on gas transfer levels with mycophenolate. Table 18.11.4.3 Disease behaviour classification Clinical behaviour Monitoring strategy Treatment goal Reversible and self-limited To remove possible triggers Short-term (3–6 months) observation to confirm disease regression Reversible with risk of progression To achieve complete or partial regression of disease and then to rationalize longer-term therapy Short-term observation to confirm treatment response; long-term observation to ensure that gains are preserved Stable with residual disease To maintain status, with or without therapy Long-term observation to assess disease course Progressive, irreversible with potential for stabilization To stabilize disease Long-term observation to assess disease course Progressive, irreversible despite treatment (i.e. a pattern of progression mimicking that of IPF) To slow progression Long-term observation to assess disease course and need for transplantation or effective palliation IPF, idiopathic pulmonary fibrosis.

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