

Review article

The respiratory system in connective tissue disorders

The connective tissue disorders (also called collagen vascular diseases) represent an heterogeneous group of immunologically mediated inflammatory disorders with a large variety of affected organs besides the lungs. The respiratory system may be involved in all its components: airways, vessels, parenchyma, pleura, respiratory muscles, etc. The frequency, clinical presentation, prognosis and response to therapy vary, depending on the pattern of involvement as well as on the underlying connective tissue disorders. The subject of this review is to describe the most frequent type of lung disorders observed in patients with connective tissue disease (CTD). We will focus on the most frequent CTD: systemic lupus erythematosus, rheumatoid arthritis, scleroderma, Sjogren's syndrome, dermatomyositis and mixed CTD.

B. Crestani

Service de Pneumologie, Hôpital Bichat-Claude Bernard, Paris Cedex, France

Key words: erythematosus; inflammatory myopathies; rheumatoid arthritis; scleroderma; Sjögren's syndrome; systemic lupus.

Professor B. Crestani
Service de Pneumologie
Hôpital Bichat-Claude Bernard
16 rue Henri Huchard
75877 Paris Cedex 18
France

Accepted for publication 8 September 2004

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune disorder which primarily affects women. SLE may affect virtually any organ and as such, the respiratory system is frequently involved by the disease. The majority of patients with SLE develop pleural or pulmonary disease in the course of their illness (Table 1). Respiratory involvement is more common in men than in women.

After 15 years of intensive use, the American College of Rheumatology classification criteria for SLE were updated in 1997 (1). The criterion 'positive LE cell preparation' was deleted, and the item 'false-positive test for syphilis' was expanded to 'positive finding of anti-phospholipid antibodies', including IgG or IgM anticardiolipin antibodies and lupus anticoagulant. Although lung involvement is not a criterion for SLE diagnosis, lung involvement has been associated with increased mortality (2, 3). The prognosis of SLE greatly improved in the past years. The results from two prospective cohorts of 1000 European (2) and 644 Canadian (4) patients with lupus found 95 and 93% 5-year survival rates, respectively.

Pleural involvement

The pleura is the most common thoracic localization of SLE. Pleural involvement may be asymptomatic although pleuritic pain is very common, affecting 45–60% of patients, and may occur without radiographically detectable chest effusion. Clinically apparent

effusions have been reported in up to 50% of patients and pathological involvement at autopsy in up to 93% of patients. Pleural involvement may be the first manifestation of SLE. Pleuritis is commonly associated with pericarditis.

Lupus pleuritis is typically associated with chest pain, dyspnea, cough and fever. The pleural effusion is uni- or bilateral, small to moderate in size (but may be massive). Thoracentesis is always needed in an SLE patient with pleural effusion as patients with SLE may have effusions for many different reasons, sometimes associated (infection, pulmonary embolism, renal failure, cardiac failure, etc.). The typical effusion is a serous or serosanguineous sterile exudate. The leukocyte differential count may show a predominance of neutrophils or mononuclear cells. Spontaneous hemothorax has been described. Biochemistry is nonspecific with increased lactate dehydrogenase and normal glucose levels. The pleural fluid antinuclear antibody assay has been said to be increased in SLE effusions although the experience is limited. Typical lupus erythematosus cells (LE cells) are seen in pleural fluid but their search is abandoned in modern clinical practice. If performed, pleural biopsy will show lymphocytes and plasmocytes pleural infiltration with some degree of pleural thickening and fibrosis. Vasculitis involving the pleural vessels is a rare finding. Pleural biopsy is indicated to exclude other etiologies, such as tuberculosis or cancer.

Spontaneous resolution of SLE effusions may occur. Lupus pleuritis is very sensitive to small doses of systemic corticosteroids, usually providing a rapid relief of

Table 1. Pleuropulmonary manifestations of systemic lupus erythematosus

Infections
Pleuritis with or without effusion
Upper and lower airways disease
Acute lupus pneumonitis
Alveolar hemorrhage
Organizing pneumonia
Chronic interstitial lung disease
Lymphocytic interstitial pneumonia
Nonspecific interstitial pneumonia
Usual interstitial pneumonia
Desquamative interstitial pneumonia
Respiratory muscle weakness (shrinking lung syndrome)
Pulmonary hypertension
Pulmonary embolism
Mediastinal lymphadenopathy

symptoms within days. Resolution of effusions may be longer. Intrapleural corticosteroids have not been adequately studied and the available experience suggests that they have a limited efficacy. Chest drainage is rarely needed as effusions are typically small. Exceptionally, pleurodesis or pleurectomy are needed for chronic effusions not controlled by medical therapy.

Pulmonary involvement

Lung parenchyma involvement in SLE may be acute or chronic.

Acute lupus pneumonitis. Acute lupus pneumonitis (Fig. 1) occurs in 1–4% of SLE patients. It often reveals a previously unknown SLE [50% of the patients in the series of Matthay et al. (5)] or may occur in the course of the disease.

The clinical presentation is nonspecific, simulating an acute infectious pneumonitis, with cough, dyspnea and fever. Hemoptysis is occasionally seen. Arterial blood gases analysis reveal hypoxemia with hypocapnia. Chest radiography and CT scan show uni- or bilateral alveolar infiltrates which usually predominate in the lower lobes. Small pleural effusions are commonly associated. Occasionally, acute respiratory failure, requiring mechanical ventilation will occur. Apart from the rare occurrence of LE cells or the detection of hematoxylin–eosin bodies, histological features obtained are nonspecific and include alveolar wall damage and necrosis, alveolar edema, hyaline membranes, inflammatory cell infiltration and alveolar hemorrhage; capillary inflammation and thrombosis are also detected; deposits of immunoglobulins and complement are variably present (6, 7).

A syndrome of acute reversible hypoxemia with normal chest X-ray films, a normal CT scan and a rapid response to corticosteroids has been described in patients with SLE (8, 9). The syndrome was attributed to leukoaggregation in the lung capillaries. Available histology data are very limited but demonstrate an infra-radiologic inflammation

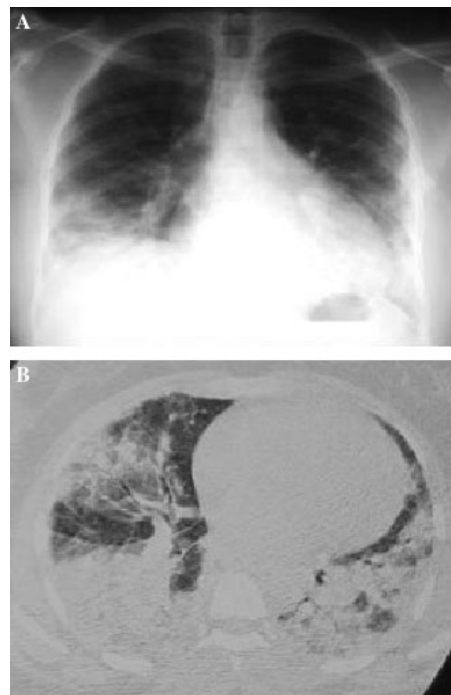


Figure 1. Acute lupus pneumonitis in a young woman. Acute respiratory failure revealed the systemic lupus erythematosus and required an admission in intensive care unit. (A) Chest radiograph showing bilateral opacities predominating in the lower lobes. (B) Computed tomography of the lungs showed bilateral consolidations predominating in the lower regions, and ground glass opacities.

in the alveolar space (9). This suggests that this syndrome is a form of less severe severity of acute lupus pneumonitis rather than a distinct entity (9).

The clinicoradiographic presentation of lupus pneumonitis is absolutely nonspecific and may simulate lung infection, pulmonary embolism, or other acute pulmonary diseases. An invasive diagnostic workup must be set up and time is crucial as acute respiratory failure and death may develop. Bronchoalveolar lavage with a search for bacterial, viral, fungal and parasitic agents is required, but empirical antibiotherapy must not be delayed as lung infections remain the first cause of pulmonary infiltrates in SLE patients. CT scan will appropriately characterize the lesions and exclude the potential diagnosis of pulmonary embolism. Lung biopsy has been advocated by some experts to exclude some diagnostics, however this procedure bears its own morbidity and mortality and lung histologic analysis is usually not diagnostic.

The treatment of acute lupus pneumonitis is based upon high doses intravenous corticosteroids (prednisone, 1–2 mg/kg/day) (10, 11). Most patients will improve with this treatment despite 50% mortality has been reported in older series (10). Pulse methylprednisolone (250–1000 mg/day for several days) have been used in patients with a severe initial presentation. Immunosuppressive or cytotoxic agents such as cyclophosphamide are used in

patients with a poor response to corticosteroids. The place of new immunomodulatory agents such as anti-TNF (12) has not been evaluated.

Diffuse alveolar hemorrhage. Diffuse alveolar hemorrhage (DAH) is a rare but severe manifestation of SLE most series reporting 50–90% mortality (10, 13, 14) although a more favorable outcome has been reported (15).

The pathogenesis of the disease is poorly understood. Immune complex-mediated injury, vasculitis with alveolar capillaritis, alveolar damage related to infection, probably play a role. The histologic findings in DAH are similar to those of acute lupus pneumonitis. Acute inflammation and necrosis involving capillaries, arterioles, and small muscular arteries has been described (16). The involvement of capillaries is manifested by an infiltrate of necrotic neutrophils within alveolar septa often associated with destruction of the alveolar wall. This capillaritis was present in all four cases originally described by Myers and Katzenstein (16), while involvement of arterioles and small arteries was seen in three. Immunofluorescence and electron microscopy demonstrated immune complexes in only two. Capillaritis is not specific of SLE as it has also been described in alveolar hemorrhage associated with the antiphospholipid syndrome, in polymyositis (PM) and other connective tissue diseases (CTD), in Henoch–Schoenlein purpura, cryoglobulinemia, and Behcet syndrome, and Wegener disease (17–19). It may also be seen in ant basement membrane antibody disease.

Zamora et al. (13) reported in 1997 their experience in Denver University hospital and reviewed the literature. DAH reveals SLE in 11–20% of the cases. Patients with lupus nephritis are at increased risk of developing DAH, and renal involvement is observed in 60–93% of the patients at diagnosis of DAH. Microvascular renal and lung involvement appear to be pathogenetically similar (20). The presentation ranges from asymptomatic to fulminant. Affected patients are young (mean age: 27 years) and present acutely ill with dyspnea, cough, fever and anemia. Symptoms are usually abrupt in onset, being present for less than 3 days in two-thirds of patients. Hemoptysis is initially present in less than half of patients. Bilateral lung infiltrates, ranging from limited ground glass opacities (Fig. 2) to dense consolidations are present. Arterial hypoxemia is common and more than 50% of the patients will need mechanical ventilation.

The diagnosis of DAH is usually easily obtained with bronchoalveolar lavage, which allows for a search for infectious agents. Concomitant lung infection, bacterial, fungal or viral, is observed in about one-third of patients, and bears a poor prognosis (13). Lung biopsy, either transbronchial or surgical, is not useful once the diagnosis of SLE is ascertained with the presence of antinuclear antibodies, and may be dangerous in critically ill patients. Echocardiography is mandatory to evaluate the presence of valvular or myocardial dysfunction.

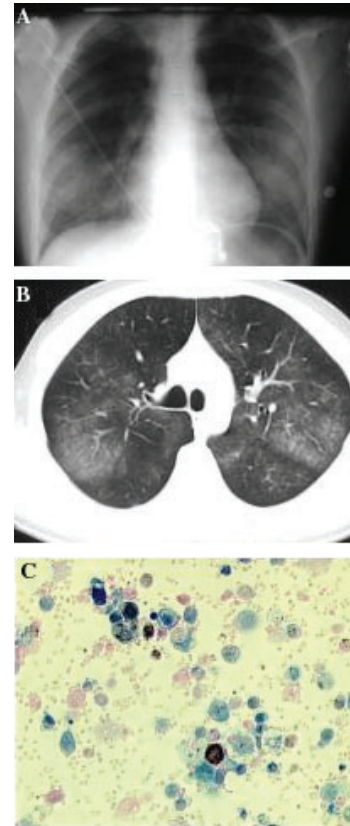


Figure 2. Diffuse alveolar hemorrhage revealed the systemic lupus erythematosus in a young man. (A) Chest radiograph showing bilateral opacities predominating in the middle regions. (B) High-resolution computed tomography of the lungs showed diffuse ground glass opacities. (C) Bronchoalveolar lavage disclosed red cells with siderophages (courtesy of Dr Homa Adle, Pathology laboratory, Hôpital Bichat-Claude Bernard).

The treatment of SLE-associated DAH is not well defined. High-dose corticosteroid alone does not appear to be very effective. In a recent series, DAH developed in patients already treated with high dose corticosteroids for lupus nephritis (14). Plasmapheresis has been anecdotally successful (21). A combination of corticosteroids, cyclophosphamide and plasmapheresis has been used with promising results (22). At this time, plasmapheresis should be reserved for patients with severe DAH refractory to corticosteroids and cyclophosphamide (23). Survivors are exposed to the risk of developing pulmonary fibrosis (24).

Chronic interstitial pulmonary disease. Clinically significant chronic interstitial pneumonia rarely complicates SLE and extensive lung fibrosis is rarely observed (3% of the patients in one study) (Fig. 3). However systematic CT evaluation of nonselected patients with SLE demonstrated the high prevalence of interstitial abnormalities, observed in 30% of the patients (25). Pulmonary function tests were abnormal in about 50% of the patients with

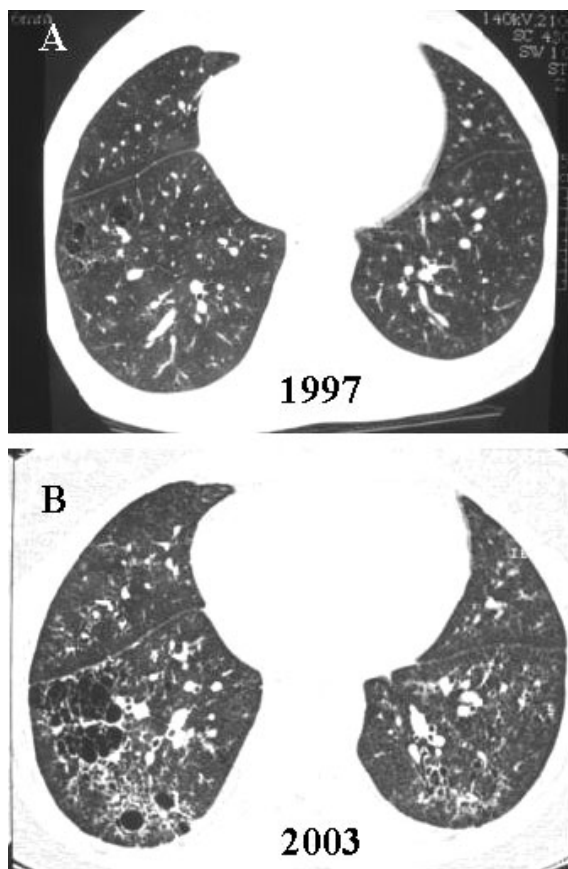


Figure 3. Evolution of pulmonary fibrosis in a patient with systemic lupus erythematosus. Between 1997 (panel A) and 2003 (panel B), lung cysts developed progressively with reticular opacities and traction bronchiectasis.

abnormal HRCT, but HRCT changes did not correlate with pulmonary function abnormalities (25). Sant et al. obtained a similar prevalence (38%) of interstitial changes on HRCT in SLE patients (26).

The larger series of Eisenberg et al. (27) described 18 patients, identified over a 1-year period, with radiographic evidence of pulmonary fibrosis, representing less than 3% of the patients followed at that institution. All the patients had a restrictive functional pattern but only seven were symptomatic. The disease develops insidiously, sometimes with mild flares of lung involvement (28). In some patients, lung fibrosis could be the sequela of acute pneumonitis. Lung involvement does not correlate with any biological characteristic, although in one series an association between anti-SS-A antibodies and chronic interstitial pneumonia was observed (29) but this observation was not confirmed in later studies which described an association between low DLCO and anti-U1 RNP antibodies (30).

Histologic reports describe nonspecific abnormalities with interstitial lymphocytic infiltrates, interstitial fibrosis, and honeycomb changes (27, 28). The place of

nonspecific interstitial pneumonia (NSIP) in SLE is not well defined (31).

Treatment is poorly evaluated. In the Weinrib's series, all patients were treated with corticosteroids, and the condition improved in nine of 14 (28). Improvement with oral methotrexate has been reported (32).

Other parenchymal diseases. Lymphocytic interstitial pneumonia (LIP) has been described in a few patients with SLE, usually associated with Sjögren syndrome (33–35). The development of lung cysts should suggest the diagnosis of LIP (33). The clinicoradiologic syndrome of organizing pneumonia (formerly known as BOOP) characterized by patchy alveolar infiltrates and an histologic pattern of organizing pneumonia has been described in patients with SLE with a good response to corticosteroids (36–38).

The simultaneous occurrence of sarcoidosis and SLE has been reported in a few cases (10). Nodular amyloidosis, excavating nodules, have also been observed.

Airway involvement

Upper airway involvement is uncommon in SLE. Laryngeal involvement is reported to occur in 0.3–13% of patients (39). The glottis and cricoarytenoid joints seem to be the most commonly involved sites, although the epiglottis and subglottis have also been reported to be involved. Laryngeal symptoms rarely present as isolated findings. Hoarseness, throat pain, and/or dyspnea all may be presenting symptoms depending on the site of involvement. SLE-related vasculitis may directly involve the larynx causing a subglottic stenosis (40).

Lower airways obstruction is not a common finding in SLE patients as evidenced by the systematic evaluation of pulmonary function tests (41) although a few cases of significant airflow obstruction have been reported.

Pulmonary vascular disease

Pulmonary hypertension. Some degree of pulmonary hypertension (PHT) complicates the course of SLE in 5–14% of the patients (42–44). PHT prevalence and mean pulmonary pressure tend to increase with time (45). In one study, PHT was associated with an overall 2-year mortality $\geq 50\%$ (46). There are only a few case reports in the literature of patients with SLE and severe PHT resulting in right heart failure. Autopsy findings from these patients have demonstrated pathologic changes of medial hypertrophy, intimal fibrosis, and plexiform lesions, which are virtually identical to the alterations seen in patients with idiopathic PHT (47). Pulmonary veno-occlusive disease, a rare form of PHT with distinct histopathology, has also been reported (48). Identification of pulmonary veno-occlusive disease is important as vasodilators are poorly tolerated in that form of disease (49). The pathophysiology of PHT is poorly understood; antiphospholipid antibodies, anti-endothelial cells

antibodies (50), vasculitis, vasospasm, and inflammation all contribute to the development of the typical proliferative lesions observed in the disease.

Raynaud's phenomenon (75%) and antiphospholipid antibodies (60%) are more common in SLE patients with PHT. Interstitial lung disease may also be more frequent (60% compared with 19% without PHT) (10).

The diagnosis of PHT is suspected on echocardiography and must be confirmed by cardiac catheterization. Exclusion of chronic thromboembolic PHT with ventilation-perfusion scintigraphy is mandatory. Treatment is based on oral anticoagulants and vasodilators. Intravenous epoprostenol has given good results (47, 51). Newer vasodilators, such as sildenafil (52) may be useful in some patients. When possible, a trial of corticosteroids and cyclophosphamide should be performed before initiating vasodilators since anecdotal responses have been reported (53).

Pulmonary embolism. A prothrombic effect of SLE separate of the antiphospholipid syndrome has been suggested but not definitely proved (54). The antiphospholipid syndrome is very common in SLE. Anticardiolipin antibodies of the IgG or the IgM isotype are found in 24 and 13% of the patients with SLE, and are associated with an increased prevalence of thrombosis (30% with IgG, 31% with IgM, vs 9% without) (55). This point is controversial as in some studies, anticardiolipin antibodies are not associated with thrombosis, but prolonged activated partial thromboplastin is (54). The antiphospholipid syndrome may develop in 50–70% of patients with both SLE and antiphospholipid antibodies after 20 years of follow-up.

Catastrophic antiphospholipid syndrome. The catastrophic antiphospholipid syndrome is a rare and excessively severe manifestation of the antiphospholipid syndrome which is observed both in primary and secondary antiphospholipid syndrome (54). The syndrome is characterized by multiple simultaneous vascular occlusions throughout the body. The lung is involved in 66% of the cases, with ARDS, pulmonary embolism, pulmonary artery thrombosis, pulmonary microthrombi, or alveolar hemorrhage, sometimes associated (56).

Pulmonary infections in SLE

Infection is a major cause of morbidity and mortality in patients with SLE, contributing for more than 50% deaths in some series. Lung infection is the most important cause of respiratory manifestations in SLE and is secondary to the immunosuppression associated with SLE itself and induced by corticosteroids and immunosuppressants. Patients with SLE are susceptible to usual pathogens and opportunistic pathogens. Mycobacterial and nocardial infections seem to be particularly important (10).

The frequent occurrence of infection mandates an aggressive approach to the SLE patient with pulmonary infiltrates. Infection should be presumed and treated empirically until an alternative diagnosis is given. Bronchoscopic lung sampling should be the rule, especially if the patient is receiving immunosuppressants.

The shrinking lung syndrome

The term 'shrinking lung syndrome' has been applied to SLE patients presenting with progressive dyspnea, the characteristic chest radiographic findings of small lung volumes, elevated hemidiaphragms and bibasilar atelectasis, with a restrictive ventilatory defect and a preserved carbon monoxide transfer coefficient. This syndrome was attributed to diaphragmatic dysfunction on the basis of the demonstration of decreased inspiratory muscle strength in 11 SLE patients (57). Conversely, Laroche et al. (58) using bilateral electrostimulation in 12 patients with the shrinking lung syndrome, failed to demonstrate diaphragm weakness. In a well-documented case, Hardy et al. described a patient with the syndrome and bilateral phrenic nerve paralysis (59). With corticosteroids, the phrenic nerve function recovered whereas the restrictive functional pattern persisted, suggesting that reduced diaphragm muscle contractility *per se* does not explain the small volume lungs and respiratory symptoms in patients with the syndrome. Hawkins reached similar conclusions in a different patient (60).

Some improvement of dyspnea and restriction has been observed with corticosteroids (10). Many patients seem to stabilize and have no worsening of lung function with time.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is the most common CTD. As is the case for SLE, the pleuropulmonary manifestations of RA are varied, pleural abnormalities and interstitial lung disease being the more common (Table 2). Although RA affects women preferentially, men are more affected by pleuropulmonary manifestations of the disease. The diagnosis of RA may be helped by novel serologic markers, more specific than rheumatoid factor: keratins antibodies (AKA) and cyclic citrullinated peptide antibodies (anti-CCP). In a recent study comparing the three antibodies, sensitivity was highest for IgM rheumatoid factor (75%), followed by anti-CCP antibodies (68%) and AKA (46%). Specificity was highest for anti-CCP antibodies (96%), followed by AKA (94%) and IgM rheumatoid factor (74%) (61).

Pleural involvement

Pleuritis and pleural effusions. Histologic pleural disease is observed in 40–70% of RA patients at autopsy (10).

Table 2. Pleuropulmonary manifestations of rheumatoid arthritis

Airways disease
Upper airways disease: cricoarytenoid arthritis
Airway obstruction
Constrictive bronchiolitis (bronchiolitis obliterans)
Bronchiectasis
Interstitial lung disease
Organizing pneumonia
Rheumatoid nodules
Caplan' syndrome
Pleural disease
Pleuritis
Pleural effusion
Pneumothorax
Bronchopleural fistula
Empyema
Vascular disease
Pulmonary hypertension
Pulmonary vasculitis
Bullous lung disease
Amyloidosis
Obstructive apnea syndrome

Pathologic findings vary. Pleural nodules, with a palisaded histiocytic reaction surrounding central areas of fibrinoid necrosis similar to that seen in rheumatoid nodules, affect preferentially the visceral pleura, so that they are rarely picked up by closed pleural biopsy. Acute inflammatory changes, pleural fibrosis or lymphoid hyperplasia are also seen.

Pleural involvement may be clinically silent. Symptomatic pleural involvement manifests with pain and/or dyspnea. Pleural chest pain occurs in 25% of RA patients; 5% of RA patients develop pleural effusions, usually small to moderate in volume, unilateral more often than bilateral. Effusions are usually spontaneously resolving within weeks, however chronic effusions are possible.

Examination of the pleural fluid is mandatory to ascertain its nature and determine its cause. Particularly, exclusion of cancer or infection is needed in patients who will receive immunosuppressants as a therapy. Pleural effusion is often opaque and milky secondary to the accumulation of cholesterol, with the biochemical characteristics of a sterile exudate. Typically, glucose concentration in pleural fluid is lower than 0.50 g/l, and lower than 0.1 g/l in 40% of patients. Low glucose level is thought to be due to a poor transport of glucose from blood to the pleura by an unknown mechanism. Low pleural fluid pH, elevated adenosine deaminase activity, elevated rheumatoid factor, increased neuron-specific enolase and soluble interleukin-2 receptor have all been associated with rheumatoid effusion, but none is specific (62, 63). Cytology shows either a neutrophilic or lymphocytic predominance.

Pleural effusions associated with RA usually do not require a specific treatment. Large pleural effusions causing dyspnea are treated with chest tube drainage and pleural sclerosis in refractory cases.

Pneumothorax, pyopneumothorax, pleural empyema. Rupture of a necrotic rheumatoid nodule in the pleura may induce a pneumothorax, or a pyopneumothorax if infected. The same mechanism probably explains the frequency of pleural empyema in RA. The treatment of these manifestations is based on chest tube drainage, with antibiotics if infection is present.

Parenchymal disease

Rheumatoid nodules. Rheumatoid nodules are the only specific lesion observed in the lung of RA patients. Rheumatoid nodules are histologically similar to that observed in the subcutaneous tissue. Occasionally, giant cells and well-formed granulomas may be observed in the peripheral region of the nodule (64). Very frequent at microscopic examination of the lung (30%), or on HRCT lung slices (20%), nodules are seldom seen on standard chest X-ray (<1%). Nodules usually predominate in the upper- and mid-lung regions, in the peripheral sub-pleural zone, although endobronchial nodules do exist. The nodules are more prevalent in males, and in patients with extra-articular manifestations or with subcutaneous nodules. Multiple widespread nodules have been described as rheumatoid nodulosis (65). Nodules are usually asymptomatic and do not evolve over time, but cavitation and infection may occur. Detection of one or more lung nodules in a patient with RA poses the problem of their nature. A systematic diagnostic workup is needed in order not to miss an infectious or tumoral lesion.

A syndrome of bilateral lung nodules in silica-exposed RA patients has been described as the Caplan's syndrome, also observed in other dust exposed RA patients (66). The histopathological image of the nodules is similar to the rheumatoid nodule except for the presence of an additional peripheral pigmented dust surrounding the lesion (64). Most patients have a preexisting mild pneumoconiosis.

Interstitial lung disease. Interstitial lung disease is the predominant pulmonary manifestation of RA. Interstitial changes are observed in 80% of lung biopsies, in up to 50% of lung CT and <5% of chest radiographs (64, 67). A decrease of the diffusing capacity of carbon monoxide is observed in up to 40% of RA patients. Bronchoalveolar lavage abnormalities are detected in 50% of asymptomatic RA patients with normal chest radiography, essentially a lymphocytic alveolitis. A neutrophil alveolitis is observed in patients with clinically evident interstitial lung disease. Symptomatic interstitial lung disease is less frequent than radiographical prevalence but the limitation of activity due to articular involvement may mask dyspnea on exercise.

Histopathological findings in RA-associated interstitial lung disease disclose very different patterns, sometimes associated: usual interstitial pneumonia (UIP), NSIP, desquamative interstitial pneumonia (DIP), LIP, organ-

izing pneumonia, eosinophilic infiltration (7). Many cases are difficult to classify into one pattern. Follicular bronchiolitis consisting of lymphoid hyperplasia and reactive germinal centers along small airways is also detected, frequently associated with an LIP pattern (31, 68). The NSIP pattern is the most prevalent (31) although in one study, UIP was the most frequent pattern (69).

HRCT pattern vary according to the histopathological pattern with a good concordance (70). The most common CT features of RA-related lung disease were ground glass opacity and reticulation (70).

The prognosis of RA-associated interstitial lung disease is usually good as the deterioration of lung function is slow. However, one study reported a median survival of 3.5 years and a 5-year survival rate of 39% in 49 patients with RA hospitalized for interstitial pulmonary fibrosis, survival very similar to what is observed in patients with idiopathic pulmonary fibrosis (71). Treatment of RA-associated interstitial lung disease is not well defined. Ideally, it should be tailored according to the pattern of lung pathologic involvement. However, lung biopsy is rarely performed in these patients and therapy is essentially empirical. Corticosteroids are first-line therapy (prednisone, 0.5–1 mg/kg) (66); responders are estimated to 40% (64). Patients with acute lung disease, with more cellular lung infiltration, with an organizing pneumonia pattern, or with eosinophilic or lymphocytic alveolitis, are more susceptible to treatment. Cyclophosphamide, azathioprine, methotrexate, cyclosporine, have been used, isolated or in association with corticosteroids for maintenance treatment or for corticosteroid resistant forms. At this time, the best treatment regimen is not defined. Treatment should be adapted to clinical, radiographic and functional tests.

Secondary amyloidosis involving the lung with an interstitial pattern is a rare but possible complication of long lasting RA (66). Apical fibrobullous disease, similar to what is observed in patients with ankylosing spondylarthritis, is observed in RA patients (72).

Airways involvement

Bronchiectasis. Bronchiectasis is fairly common in RA (Fig. 4). HRCT studies demonstrate that 20–35% of RA patients present bronchiectasis (associated with interstitial changes in one-third of the cases) (73). However, autopsy data report lower numbers (5–12% of RA patients) and clinically significant bronchiectasis is less frequent, involving 1–5% of RA patients. In most patients (90%), bronchiectasis precedes the development of RA by 25–30 years. Secondary development of bronchiectasis after 7–10 years of evolution of RA is possible. Bronchiectasis is more common in women than in men (2.8 women/1 man), as is the case for RA (74). In some studies, RA appears at a younger age in patients with bronchiectasis (46 vs 51 years). The co-existence of RA and bronchiectasis is associated with an alteration of



Figure 4. Bronchiectasis predominating in the left lower lobe in a 40-year-old woman with rheumatoid arthritis. The bronchi in the left upper lobe and the right lower lobe were also abnormal. The patient presented with recurrent bronchial infections and *Pseudomonas aeruginosa* colonization of the airways.

lung function tests (73) and a poor 5-year survival (75). In a case–control study, patients with RA and bronchiectasis were 7.3 times more likely to die than the general population, 5.0 times more likely than patients with RA and 2.4 times more likely than patients with bronchiectasis without RA (75). An increased risk of death within the RA and bronchiectasis group was associated with a history of smoking, more severe RA and steroid usage (75); in that study, 60% of the mortality was due to infections and acute respiratory failure. Bronchiectasis probably favors lung infections, a major cause of death in RA (76). Bronchiectasis also increases the postoperative morbidity in RA patients (77).

The reasons for an increased prevalence of bronchiectasis in RA are poorly understood. Patients with RA have an increased susceptibility to airway infections perhaps due to a defect in humoral immunity (78). The yellow nail syndrome, which associates recurrent bronchial and rhinosinusal infections, pleural effusions, lymphedema and typical changes of the nail has been described in RA (79). A search for some genetical risk factors was not fruitful: bronchiectasis in RA patients has been associated with some DR1 haplotypes and with DQB1*0601, *0301, *0501 (80). An excess of heterozygous mutations in the cystic fibrosis transmembrane regulator (CFTR) gene has been described (81). Sjögren's syndrome (SS) does not seem to be overrepresented in patients with RA and bronchiectasis.

Airway obstruction. Controlled studies of lung function in RA patients demonstrate an increased prevalence of chronic airway obstruction (16–38% of RA patients) (82, 83) and an increased bronchial reactivity to metacholine (55% of RA patients in one study) (84). Patients may benefit of a treatment with inhaled corticosteroids and bronchodilators. Pathology studies demonstrate different patterns of airways involvement: follicular bronchiolitis,

constrictive bronchiolitis, diffuse panbronchiolitis (85). Despite the high prevalence of lung function abnormalities, severe airways obstruction in nonsmoking RA patients is a rare finding, which is clearly more frequent in patients treated with D-penicillamine even in non-RA patients (86), although it may be observed in RA without D-penicillamine treatment (87). The associated histology pattern is constrictive bronchiolitis (previously bronchiolitis obliterans). The prognosis is poor with 50% mortality within a few months.

Cricoarytenoid arthritis. Cricoarytenoid arthritis is a frequent (26% of RA patients in one study) (88) and overlooked manifestation of RA that may present with poorly defined symptoms: sensation of foreign body in the throat, sore throat, hoarseness, fullness in the throat, dyspnea, difficulty with inspiration, pain radiating to the ears, stridor, dysphagia, odynophagia, and pain with speech (66). The diagnosis is clinically evident with direct or indirect laryngoscopy showing inflammatory changes of the arytenoids (erythema, swelling, thickening of mucosa) with reduced motility. CT scan confirms the diagnosis (89). In some cases, ankylosis of the cricoarytenoid joint may induce an upper airway obstruction with a characteristic pattern on the flow-volume curve. Cricoarytenoid arthritis is treated with anti-inflammatory medications. In patients with dyspnea, surgery may be

needed. Cricoarytenoid arthritis may favor obstructive sleep apnea which is more frequent in RA patients.

Vascular involvement

Lung vascular involvement is a rare finding in patients with RA. PHT resembling idiopathic PHT has been associated with RA (90). Alveolar haemorrhage related to pulmonary vasculitis has been reported (91), sometimes with antineutrophil cytoplasmic antibodies (92).

Drug-induced lung disease

Several drugs used for the treatment of RA have been associated with drug-induced lung disease. Undesirable respiratory side effects of methotrexate (Fig. 5), gold salts, D-penicillamine, and nonsteroidal anti-inflammatory drugs are very well described. However, new compounds (such as anti-TNF, sirolimus, leflunomide), and new clinicoradiological patterns are continuously described. Reference to available comprehensive reviews (93, 94) and to Pneumotox[®] (www.pneumotox.com), an internet searchable database which gives up-to-date information for this rapidly evolving field (95) are needed in order to determine whether any respiratory abnormality in a RA patient could be secondary to the treatment received.

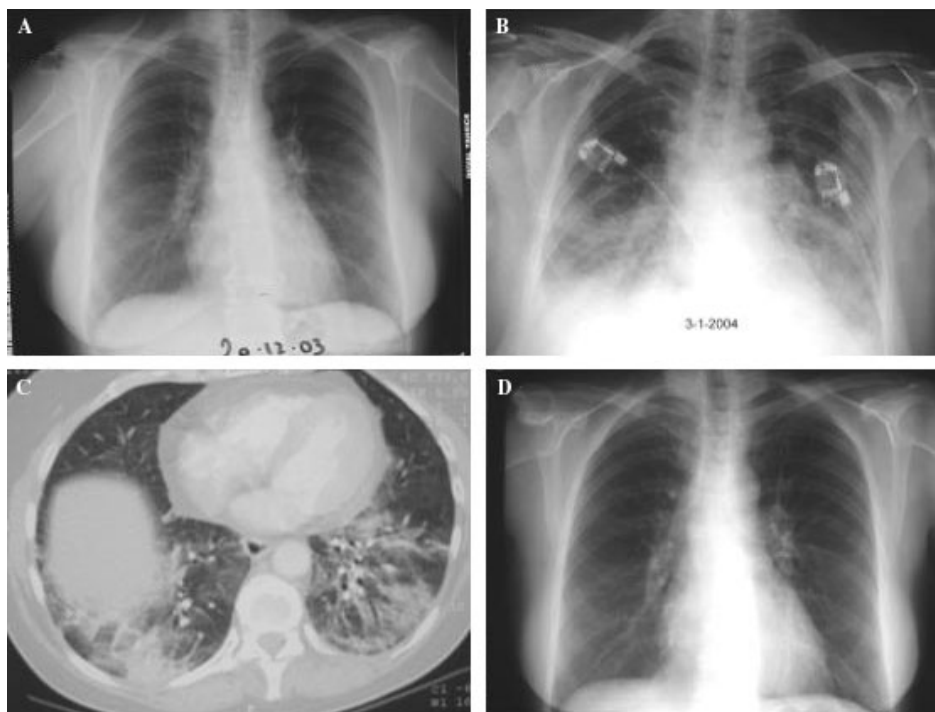


Figure 5. Methotrexate pneumonitis in a patient with rheumatoid arthritis. Progressive respiratory failure with high fever developed within 2 weeks (panel A: initial radiograph) and required an admission in intensive care unit (panel B). Computed tomography of the lung showed bilateral alveolar opacities (panel C). Methotrexate was stopped, methylprednisolone was given because of profound hypoxemia and chest radiograph normalized within 1 week (panel D).

Sjögren's syndrome

The SS is one of the most common autoimmune diseases, characterized by the infiltration of different organs by CD4-positive T lymphocytes, the lacrimal and salivary glands being the most often involved (96). The classic triad associates xerostomia (dry mouth), xerophthalmia (dry eyes) and arthritis. Multiple diagnosis criteria have been proposed, and have been recently updated (97). Criteria now require the presence of either an anti-SSa or anti-SSb autoantibody, or a typical lesion on the accessory gland biopsy (Chisholm grade 3 or 4). SS may be isolated (primary SS) or associated with a definite CTD (secondary SS, primarily with RA). Lung involvement is less common and less severe in primary SS than in secondary SS.

The reported prevalence of pulmonary disease in SS varies widely according to the diagnostic modalities used to identify the abnormalities. HRCT detects abnormalities in 34–65% of SS patients evaluated (98, 99). A comprehensive evaluation including lung function tests detected abnormalities in 75% of SS patients (100). However, if one considers only clinically significant pulmonary disease, it is estimated to affect less than 10% of SS patients (101, 102). Airways involvement and interstitial lung disease are the most frequent manifestations of lung involvement in SS (Table 3).

Airways involvement

Lymphocytic infiltration involves the entire respiratory tract from nares to bronchioles and alveoli (103, 104). Symptoms are thought to be secondary to the desiccation

of the respiratory tract, to abnormalities of the mucociliary clearance and to the chronic inflammatory state of the airways, although some patients have no symptoms despite lymphocytic infiltration of the bronchial mucosa. Upper respiratory tract involvement manifests as dryness, crusting, recurrent infections, nasal septal perforation, and recurrent otitis media. Lower airways involvement will produce a dry irritating cough, observed in up to 50% of the patients (105), and recurrent bronchial and pulmonary infections in about 20% of the patients (105).

Many studies have evaluated obstructive airway disease in SS patients. Although one study found no evidence of obstructive airway disease when compared with control populations (106), most of the studies using sensitive tests observed abnormal expiratory flows in patients with SS (96). The clinical importance of these abnormalities remains unproven. Bronchial hyperactivity is detected in 40–60% of SS patients (107); its mechanism is probably different from asthma-associated hyperactivity as it is not controlled by inhaled corticosteroids (108). HRCT studies confirm the prevalence of bronchial changes in SS with quite different prevalence values in different studies: bronchial mucosa thickening (8–68%), bronchiolar nodules (6–29%), bronchiectasis (5–42%), air trapping (32%) (99, 109–112).

Interstitial lung disease

Interstitial lung disease is common in patients with SS and may reveal the disease. It affects 8–38% of patients with primary SS. The histopathology of interstitial lung disease in SS is not specific. Different histological patterns may be observed, sometimes associated in a given individual: NSIP, UIP, LIP, follicular bronchiolitis, organizing pneumonia, end-stage lung (7, 31, 98, 113). NSIP is the more common pattern (31, 113). Well-formed granulomas may be seen in up to 10% of samples. Accordingly, the HRCT pattern in SS is not specific. However, cystic lesions are reported in about 30% of the patients with SS, often associated with LIP (114). Cysts form as a consequence of bronchiolar obstruction due to follicular bronchiolitis, and sometimes bullous destruction of the lung occurs (114).

Bronchoalveolar lavage has demonstrated the high prevalence of subclinical lymphocytic and neutrophilic alveolitis, affecting 50% of SS patients (115). Alveolitis is more frequent in patients with extra-pulmonary involvement. An expansion of CD8+ T-lymphocytes has been associated with more frequent alteration of lung function tests (116). Neutrophilic alveolitis was associated with alterations of lung function tests (117).

Information concerning the evolution and the treatment of interstitial lung disease in SS are limited. Available data suggest that interstitial lung disease in primary SS has a good prognosis without evidence of clinically significant deterioration over time (102, 105, 118, 119), although progression of lung disease is more

Table 3. Pleuropulmonary manifestations of Sjögren's syndrome

Nasal mucosa desiccation
Airways disease
Tracheobronchial desiccation
Obstructive lung disease
Follicular lymphocytic bronchitis and bronchiolitis
Bronchiectasis
Interstitial lung disease
Lymphocytic interstitial pneumonia
Non specific interstitial pneumonia
Usual interstitial pneumonia
Desquamative interstitial pneumonia
Alveolar disease
Lymphocytic alveolitis
Malignancy
Lymphoma
Pseudolymphoma
Pleural disease
Pleural effusion
Pleuritis
Pleural thickening
Others
Pulmonary hypertension
Bullous lung disease

likely to occur in patients with BAL fluid neutrophilia (117) or with an abnormal HRCT of the lung (119).

Hydroxychloroquine has been shown to reduce sicca symptoms in a retrospective study (120) but its effect on pulmonary involvement was not evaluated. Organizing pneumonia in the context of SS respond quite well to corticosteroids. The response of LIP to corticosteroids and immunosuppressive therapies is not well described in the literature. The evolution of other forms of interstitial lung disease is poorly documented. Deheinzeln reported the evolution of 11 patients treated with azathioprine alone or combined with prednisone (98). The condition of seven patients improved (symptomatic relief and increase of FVC) and one patient deteriorated. Among five untreated patients, only one improved. The respective position of these treatments is not clear but a trial of prednisone and azathioprine should be performed in symptomatic patients.

Pulmonary lymphoma

Patients with SS have an increased risk of developing a lymphoma (relative risk: 33–44). The risk is maximal for primary SS ($\times 2$). Sjögren's associated lymphoma is usually a B-cell non-Hodgkin's lymphoma which arise primarily in the salivary glands, but also in mucosal sites including stomach and the lung. Pulmonary lymphoma will affect 1–2% of all patients with SS (96). Pulmonary involvement occurs in 20% of the patients with Sjögren's associated lymphoma (121, 122). Radiographical presentation may vary: chronic alveolar opacities, reticular or reticulonodular opacities, diffuse nodular lesions, or pleural effusion with or without mediastinal disease (96). Pulmonary lymphoma may be indolent and surgically removed (123), may be controlled with cytotoxic drugs such as chloraminophene or cyclophosphamide, and may evolve to an aggressive disease requiring a systemic polychemotherapy with monoclonal B-cell antibodies (124). The nature and existence of pseudolymphoma, a tumor-like aggregate of lymphoid cells that does not meet the criteria for malignancy, is debated.

Others

Pleural thickening and pleural effusions are uncommon in SS and should be investigated to determine their specific cause (lymphoma, tuberculosis, etc.). PHT (125), pulmonary amyloidosis, the association of sarcoidosis with SS (126), diaphragmatic dysfunction, have been described.

Systemic sclerosis (scleroderma)

Pulmonary involvement in systemic sclerosis (SSc) is very common, both clinically and at autopsy, and bears a poor prognosis (Table 4). Pulmonary complications are now

Table 4. Pleuropulmonary manifestations of systemic sclerosis

Pulmonary hypertension
Interstitial lung disease
Non specific interstitial pneumonia
Usual interstitial pneumonia
Lymphocytic interstitial pneumonia
Organizing pneumonia
Pneumoconiosis (silicosis)
Alveolar hemorrhage
Pleural involvement
Bronchogenic carcinoma
Respiratory muscle weakness
Aspiration pneumonia
Small airways disease

the first cause of death in SSc (127). Interstitial lung disease with progressive fibrosis is the most common pulmonary disease, affecting 75% patients at autopsy, followed by PHT, affecting up to 50% of SSc patients (128). Systemic involvement usually appears within 5 years of diagnosis (essentially within 2 years), but later appearance is also possible and thus justify a close follow-up of these patients.

Two forms of SSc have been individualized with characteristic clinical presentation, autoimmune signature and evolution. Limited SSc (70% of all SSc patients) is characterized by distal cutaneous sclerosis (below the knees, the elbows, and not affecting the thorax), a long history of Raynaud's phenomenon before the diagnosis and the presence of circulating anticentromere antibodies (positive in 70% patients). Its typical form consists in the CREST syndrome with subcutaneous calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias predominating on the face and the thorax. PHT typically occurs in patients with limited SSc. Survival has been estimated at 98% at 1 year, 80% at 6 years and 50% at 12 years after diagnosis (129).

Diffuse SSc (30%) is characterized by the proximal involvement of the skin, extending to the thorax. Cutaneous involvement occurs simultaneously to the appearance of the Raynaud's phenomenon. Antitopoisomerase antibodies are present in 30% of the patients, whereas anticentromere antibodies are usually absent (detected in 3% of the patients with diffuse SSc). Pulmonary fibrosis typically affects patients with diffuse SSc. Survival was poor: 80% at 1 year, 30% at 6 years, 15% at 12 years (129) but recent data suggest an improvement of the prognosis (130).

The pathophysiology of SSc is poorly understood, particularly the link between autoimmunity and fibroproliferation does not appear clearly. It may be the consequence of endothelial lesions.

Interstitial lung disease

Interstitial lung disease may occur in limited or diffuse SSc. The onset of pulmonary involvement is usually

progressive and rarely precedes scleroderma although a syndrome called SSc sine scleroderma has been described in men exposed to inhaled mineral particles (131). About 25% of SSc patients will develop clinically significant interstitial lung disease and 13% a severe restrictive lung disease (132).

For many years, idiopathic pulmonary fibrosis and pulmonary fibrosis associated with SSc were viewed as histologically similar, contrasting with the very different prognosis of the two diseases (133). It is now clearly evident that NSIP is the main histological pattern in interstitial lung disease associated with SSc (134–136), UIP being the pattern associated with idiopathic pulmonary fibrosis (137). Bouros et al. evaluated the histopathology of surgical lung biopsies from 80 patients with lung fibrosis and SSc (136). NSIP ($n = 62$, 77.5%), subcategorized as cellular NSIP ($n = 15$, 24%) and fibrotic NSIP ($n = 47$, 76%) was much more prevalent than UIP ($n = 6$), end-stage lung disease ($n = 6$), or other patterns ($n = 6$) (136). In that study, 5-year survival differed little between NSIP (91%) and UIP/end-stage lung disease (82%). Outcome was linked more strongly to disease severity at presentation and serial DLCO trends than to histopathologic findings (136). This result contrasts with those obtained by Kim et al. who observed in a series of 19 patients that the outcome was better in patients with NSIP than UIP (135).

Deterioration of pulmonary function tests (a restrictive ventilatory defect and reduced DLCO) are arguments for a poor prognosis. Evolution of DLCO over the first year after diagnosis has a strong prognostic value (136).

HRCT of the lung is the best tool to identify pulmonary fibrosis in SSc (Fig. 6) (138). Abnormalities



Figure 6. Diffuse opacities in a woman with diffuse systemic sclerosis. Traction bronchiectasis suggest that fibrosis is present. Note the esophageal dilation with an air-fluid level.

predominate in the basal and subpleural regions of the lungs, and combine reticular and ground glass opacities with honeycombing. Ground glass opacities are usually the predominant abnormality; they consist more of fine intralobular fibrosis than true alveolitis (139, 140). Disease extent on HRCT has a strong prognostic value.

Bronchoalveolar lavage has been extensively evaluated in patients with SSc. BAL lymphocytosis in SSc is associated with secondary SS and has a relatively better prognosis. BAL neutrophilia has been consistently associated with progressive disease as assessed by deterioration of lung function (141–143). However, whether BAL neutrophilia is an independent factor for predicting progression of interstitial lung disease in SSc when other prognostic factors (such as pulmonary function tests and the extent of fibrosis on HRCT) are taken into account is debated (138). BAL eosinophilia bears a poor prognosis in one study (136).

The treatment of lung involvement in SSc is poorly defined. Indeed, controlled studies are lacking. Current data suggest that cyclophosphamide, either oral (143) or intravenous (144–146), with low dose corticosteroids, stabilizes or improves lung function tests and HRCT, with subsequent decline in most patients after stopping cyclophosphamide. Unresolved issues concern the dose of corticosteroids to be administered with cyclophosphamide, the optimal dose and duration of cyclophosphamide, the optimal immunosuppressive treatment after initial cyclophosphamide treatment. A combination of low dose prednisone and azathioprine is often given after 12 months of cyclophosphamide. Hypofertility is possible after cyclophosphamide treatment and patients should be given the possibility to store ova or sperm in view of future procreation. The decision when to begin treatment is difficult. The best criteria is probably the evidence of progression on successive evaluation (138).

There is limited evidence for an antifibrotic activity of cyclosporine (147) or D-penicillamine in the lung (148). Other treatments are being prospectively evaluated, such as bosentan (antagonist of ETA and ETB endothelin receptors) or autologous stem cell transplantation (149). Lung transplantation has been successfully performed in patients with SSc. Esophageal dysmotility induces specific postoperative complications.

Pulmonary hypertension

PHT is defined by mean pulmonary artery pressure ≥ 25 mmHg at rest, or ≥ 30 mmHg at exercise. PHT affects 5–33% of SSc patients, depending on the diagnostic criteria used. Clinically severe PHT affects 9% of CREST patients (150). Severe PHT usually occurs in patients with the limited cutaneous form of the disease, although it may also be observed in patients with diffuse SSc in association with pulmonary fibrosis. In the later situation, PHT is rarely severe (mPAP < 35 mmHg). PHT is a late complication of SSc, occurring 7–9 years after diagnosis.

Pathology shows fibrosis of the intima, hypertrophy of the media, and plexogenic arteriopathy as observed in idiopathic PHT (151). A mononuclear inflammatory infiltrate may be seen (152).

Invasive hemodynamic study is the gold standard diagnostic test. It has been suggested to perform an invasive hemodynamic study in patients with suspected raised pulmonary artery systolic pressures of >35 mmHg, carbon monoxide transfer factor (TLCO) $<50\%$ predicted, or a precipitous fall in TLCO $>20\%$ over a 1-year period with no pulmonary fibrosis, and patients with SSc with breathlessness with no pulmonary fibrosis (153). Doppler-echocardiography has a good positive predictive value but it cannot be used safely to exclude PHT in patients with an high prediagnostic probability as is the case in patients with SSc (153, 154). Echocardiography must be performed annually in patients with SSc.

The natural history of PHT is almost always progressive deterioration with death. In a recent series, survival was 81, 63, and 56% at 1, 2, and 3 years from the diagnosis (153). Hemodynamic indices of right ventricular failure: raised mRAP (hazard ratio: 21), raised mPAP (hazard ratio: 20), and low CI (hazard ratio: 11) predicted an adverse outcome. There was no significant difference in survival between patients with SSc PHT with and without pulmonary fibrosis.

Treatment of PHT in SSc is linked to the evidence obtained in idiopathic PHT. Physical effort and pregnancy must be avoided because of the risk for acute right ventricle failure and death. Warfarin is recommended. Supplemental oxygen is given in patients with hypoxemia ($\text{PaO}_2 < 60$ mmHg). Diuretics may be used in patients with edema. Vasodilators may be useful in patients with a significant vasodilatory response with inhaled nitric oxide testing: nifedipine and diltiazem are the most useful drugs (155). High doses are needed: nifedipine 90–180 mg/day and diltiazem 360–720 mg/day. The use of lower doses is not effective. Angiotensin-converting enzyme inhibitors are not useful in this context. Continuous infusion of prostacyclin (epoprostenol) or its analog isoproterenol improves hemodynamic parameters and the effort capacity although the effect on survival is uncertain (156). In the experience of the Antoine Bécclère center (Clamart, France), survival in patients with CREST syndrome-associated PHT appeared to be lower than in patients with the idiopathic form of the disease (157). Acute pulmonary edema may occur at the initiation of vasodilators in patients with veno-occlusive disease or capillary hemangiomatosis (158) both abnormalities may be observed in patients with SSc. Oral, inhaled or subcutaneously administered analogs of prostacyclin have been developed and demonstrate beneficial effects in PHT, either idiopathic or associated with CTD (156). The effect is always limited in the latter compared with the former. Bosentan, an oral ETA and ETB endothelin receptors antagonist, prevented deterioration in the walking

distance among patients with scleroderma-associated PHT (159). Successful treatment of SSc digital ulcers and pulmonary arterial hypertension with bosentan has been reported (160). Therapeutic trials using sildenafil are underway (161). Anecdotal case reports indicate that immunosuppressants improve PHT associated with CTD, SLE and MCTD rather than scleroderma. A trial of corticosteroids and cyclophosphamide should be performed in patients with PHT under a strict clinical and hemodynamic control. Lung transplantation is possible in case of epoprostenol failure (162).

Lung cancer

Lung cancer incidence is increased four- to 16-fold in patients with SSc compared with the general population and may affect up to 4% of SSc patients (163, 164). This is similar to the increased risk observed in patients with idiopathic pulmonary fibrosis. Lung cancer occurs essentially in patients with pulmonary fibrosis (Fig. 7) and is not related to tobacco smoke. Adenocarcinomas of the bronchoalveolar type are overrepresented but all cell types are observed. The mechanisms of this association are not perfectly understood.

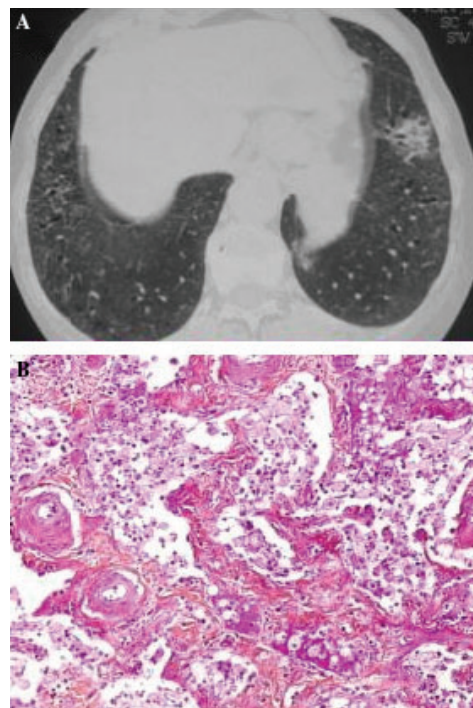


Figure 7. A poorly defined nodule was detected in the left lower lobe in a woman with the CREST syndrome (panel A: high-resolution computed tomography of the lung). She had smoked for 30 years. Note the presence of reticular opacities in the lower lobes. A lobectomy was performed and detected a bronchioloalveolar carcinoma (panel B, courtesy of Dr Homa Adle, Pathology laboratory, Hôpital Bichat-Claude Bernard).

Others

Organizing pneumonia, alveolar hemorrhage, sarcoidosis, cystic lung disease, pneumothorax, and respiratory muscle dysfunction have been observed repeatedly in patients with SSc (128). Aspiration pneumonia is especially frequent in patients with severe esophageal dysfunction.

Polymyositis and dermatomyositis

The inflammatory myopathies are often included in the field of the CTD. Among these, PM and dermatomyositis (DM) are those which are particularly associated with pulmonary involvement (Table 5). Pulmonary involvement may precede by many years, or occur simultaneously or follow the muscular manifestations of PM–DM (165). In this context, the antisynthetase syndrome has been isolated and must be recognized because of the high prevalence of pulmonary disorders (166). This syndrome includes PM or DM (63–100%), interstitial lung disease (40–100%), Raynaud’s phenomenon (25–100%), thick cracked skin over the tips and sides of the fingers (mechanics hands), and the presence of one of the seven identified antisynthetase antibodies (Table 6). Severe constitutional symptoms are common, with fever in 80% of the patients, asthenia and weight loss. Interstitial lung disease with CD8+ lymphocytic alveolitis without muscle involvement may be observed (167). Five to 8% of cases in the antisynthetase syndrome manifest as overlap syndromes with other CTD including RA, lupus, scleroderma, and SS (166). The antisynthetase syndrome carries a poor prognosis that seems related to the severity and frequent steroid resistance of interstitial lung disease.

Different elements of the respiratory system may be involved in patents with PM/DM: respiratory muscles dysfunction (168), interstitial lung disease, lung cancer, aspiration pneumonia in patients with pharyngolaryngeal muscles involvement, PHT (169). Cardiac involvement is common and may induce dyspnea and chest X-ray abnormalities. Pulmonary involvement is a predominant cause of death, due to aspiration pneumonia (particularly

Table 6. Antisynthetase antibodies with their cellular target

Antibody	Cellular target
Anti-Jo1	Anti-histidyl-tRNA synthetase
Anti-PL7	Anti-threonyl-tRNA synthetase
Anti-PL12	Anti-alanyl-tRNA synthetase
Anti-OJ	Anti-isoleucyl-tRNA synthetase
Anti-EJ	Anti-glycyl-tRNA synthetase
Anti-KS	Anti-asparaginyl-tRNA synthetase
Anti-Wa	48 kDa protein bound to acetylated tRNA

in elderly patients) (170), to the evolution of pulmonary fibrosis or to lung cancer (171).

Interstitial lung disease

Interstitial lung disease affects 20–30% patients and is usually present at the time of diagnosis (165, 172–174). Antisynthetase antibodies are detected in 40% (172, 173) to 80% (175) of the patients with PM and interstitial lung disease (anti-Jo1 being the most frequent). Anti-Jo1 is present in 23% of all patients with PM. Arthritis is more common in PM-DM with ILD (173, 176). Pulmonary involvement bears a poor prognosis leading to the death with respiratory insufficiency 30–66% of patients (Fig. 8).

Interstitial lung disease may take several forms:

1. An acute respiratory failure evolving in a few days or weeks with fever, bilateral and basal infiltrative opacities and a negative search for pathogens and a failure of empirical antibiotics. Histopathology reveals a diffuse alveolar damage (177). The prognosis is usually poor without improvement despite aggressive corticosteroids and immunosuppressants treatment. Some forms are responsive to corticosteroids. In that case, histopathology reveals NSIP, or organizing pneumonia (178). Sometimes, the clinical pattern is that of an acute alveolar hemorrhage with pulmonary capillaritis (19).

2. A progressive fibrosing interstitial lung disease with cough and dyspnea. In that case, NSIP has been shown to be the predominant pattern (65–80%, predominantly fibrotic or mixed forms), much more frequent than UIP, organizing pneumonia or LIP pattern (31, 172, 174). About 25% of the patients will deteriorate their lung function at follow-up (173). The evolution of HRCT abnormalities was recently described in 14 patients with PM/DM and NSIP (mean follow-up period, 27 months) (179). Predominant findings on the initial CT scans were of reticular and/or ground-glass opacities with or without consolidation. Reticular and ground-glass opacities predominated in the lower zone of each lung, and consolidation predominated at the lung periphery. With treatment, serial CT scans showed significant improvement of ground-glass and reticular opacities (in 11 and 13 patients, respectively). In one patient, ground-glass opacity progressed, and death occurred after 3 months. Traction bronchiectasis was seen in 12 patients, and it improved in four patients after treatment. Honeycomb

Table 5. Pleuropulmonary manifestations of polymyositis and dermatomyositis

Interstitial lung disease
Non specific interstitial pneumonia
Usual interstitial pneumonia
Lymphocytic interstitial pneumonia
Organizing pneumonia
Diffuse alveolar damage
Alveolar hemorrhage with pulmonary capillaritis
Pleural involvement
Bronchogenic carcinoma
Respiratory muscle weakness
Aspiration pneumonia
Pulmonary hypertension

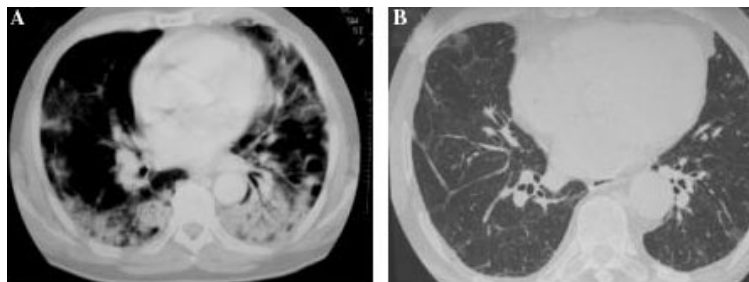


Figure 8. Organizing pneumonia in a patient with the antisynthetase syndrome (anti-Jo1 antibody). (panel A) Computed tomography of the lung: bilateral consolidations areas with alveolar bronchogram. (panel B) Rapid improvement with corticosteroids.

lung was not noted in any patient during follow-up. Retrospective studies suggest that patients with progressive interstitial lung disease are characterized with honeycombing (180), extensive ground-glass opacities and BAL neutrophilia (181).

Pulmonary function tests indicate a restrictive defect with reduced diffusing capacity for carbon monoxide, and hypoxemia at rest. Exercise testing is of importance in PM-DM patients to elucidate the cause of dyspnea. In some patients, the radiograph will detect lung infiltrates in a patient without symptoms. Alternatively, HRCT may demonstrate an interstitial lung disease in a patient with normal radiograph.

Corticosteroids are used for initial treatment (prednisone 40–60 mg/day). Oral or intravenous cyclophosphamide allow to stabilize lung function in patients with a progressive disease. In patients with a nonprogressive disease, mild immunosuppressive treatment based on azathioprine or methotrexate allows for a fair control of the disease (172). In refractory cases, methylprednisolone pulses, cyclosporine, and tacrolimus have been successfully used (182). Although useful in refractory PM, intravenous immunoglobulins have not been evaluated for their effect on lung involvement (183).

Lung cancer

About 15% of patients with PM-DM have a diagnosis of cancer in their medical history (184). Lung cancer is one of the most frequent. Both PM and DM increase the risk of having a lung cancer and the risk is maximal for DM [standardized index ratio for DM: 5.9 (3.7–9.2), for PM: 2.8 (1.8–4.4)] (184). Most of the cases (70%) occur after the diagnosis of PM/DM. The risk is maximal in the first year of diagnosis but persists for 5 years in PM, and even more for DM.

Mixed connective tissue disease

Patients with mixed connective tissue disease (MCTD) exhibit clinical features of SLE, progressive SSc, and

PM-DM (185). A prerequisite for the diagnosis of MCTD is the presence of high titers of antibodies against uridine-rich RNA-small nuclear ribonucleoprotein (anti-RNP). The identification of MCTD as a separate entity remains debated as many patients initially diagnosed MCTD will evolve into a definite disease within 5 years (185). Although they were not reported in the original publication on MCTD, pleuropulmonary manifestations are common in MCTD and the incidence varies from 20 to 85% (185). Respiratory and nonrespiratory features of the disease follow those seen in SLE, scleroderma, or PM-DM. Major respiratory manifestations include interstitial lung disease and pulmonary fibrosis (20–65%), pleural effusion (50%), and PHT (10–45%). Other pulmonary features consist of pulmonary vasculitis, pulmonary thromboembolism, pulmonary infections (secondary to aspiration pneumonia due to esophageal motility alterations and immunosuppression), alveolar hemorrhage, pulmonary nodules, pulmonary cysts, mediastinal lymphadenopathy, and respiratory muscles dysfunction. PHT is a major cause of mortality and morbidity. Principles for diagnosis and treatment are similar to those described for SLE, scleroderma, and PM-DM.

Conclusion

Involvement of the respiratory system is a common event in CTD. Although some characteristic clinical and radiological patterns are recognized, most of lung disorders may affect any type of CTD. Respiratory symptoms in a patient with a known CTD require a prompt and systematic work-up in order to diagnose specific diseases, and not to miss frequent and nonspecific cardiorespiratory problems, such as pulmonary infections, pulmonary embolism, and left ventricular failure. Rare conditions such as drug-induced respiratory manifestations may prove difficult to diagnose. Conversely, every practitioner must have a high level of suspicion toward CTD as these diseases can masquerade as very common disorders.

References

1. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;**40**:1725.
2. Abu-Shakra M, Urowitz MB, Gladman DD, Gough J. Mortality studies in systemic lupus erythematosus. Results from a single center. II. Predictor variables for mortality. *J Rheumatol* 1995;**22**:1265–1270.
3. Stoll T, Seifert B, Isenberg DA. SLICC/ACR Damage Index is valid, and renal and pulmonary organ scores are predictors of severe outcome in patients with systemic lupus erythematosus. *Br J Rheumatol* 1996;**35**:248–254.
4. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P et al. Morbidity and mortality in systemic lupus erythematosus during a 5-year period. A multicenter prospective study of 1,000 patients. European Working Party on Systemic Lupus Erythematosus. *Medicine (Baltimore)* 1999;**78**:167–175.
5. Matthay RA, Schwarz MI, Petty TL. Pulmonary manifestations of lupus erythematosus: review of twelve cases of acute lupus pneumonitis. *Medicine (Baltimore)* 1975;**54**:397–409.
6. Haupt HM, Moore GW, Hutchins GM. The lung in systemic lupus erythematosus. Analysis of the pathologic changes in 120 patients. *Am J Med* 1981;**71**:791–798.
7. Colby TV. Pulmonary pathology in patients with systemic autoimmune diseases. *Clin Chest Med* 1998;**19**:587–612.
8. Abramson SB, Dobro J, Eberle MA, Benton M, Reibman J, Epstein H et al. Acute reversible hypoxemia in systemic lupus erythematosus. *Ann Intern Med* 1991;**114**:941–947.
9. Susanto I, Peters JI. Acute lupus pneumonitis with normal chest radiograph. *Chest* 1997;**111**:1781–1783.
10. Murin S, Wiedemann HP, Matthay RA. Pulmonary manifestations of systemic lupus erythematosus. *Clin Chest Med* 1998;**19**:641–665.
11. Raj R, Murin S, Matthay RA, Wiedemann HP. Systemic lupus erythematosus in the intensive care unit. *Crit Care Clin* 2002;**18**:781–803.
12. Aringer M, Smolen JS. Tumour necrosis factor and other proinflammatory cytokines in systemic lupus erythematosus: a rationale for therapeutic intervention. *Lupus* 2004;**13**:344–347.
13. Zamora MR, Warner ML, Tuder R, Schwarz MI. Diffuse alveolar hemorrhage and systemic lupus erythematosus. Clinical presentation, histology, survival, and outcome. *Medicine (Baltimore)* 1997;**76**:192–202.
14. Liu MF, Lee JH, Weng TH, Lee YY. Clinical experience of 13 cases with severe pulmonary hemorrhage in systemic lupus erythematosus with active nephritis. *Scand J Rheumatol* 1998;**27**:291–295.
15. Schwab EP, Schumacher HR Jr, Freundlich B, Callegari PE. Pulmonary alveolar hemorrhage in systemic lupus erythematosus. *Semin Arthritis Rheum* 1993;**23**:8–15.
16. Myers JL, Katzenstein AA. Microangiitis in lupus-induced pulmonary hemorrhage. *Am J Clin Pathol* 1986;**85**:552–556.
17. Falk RJ, Hogan S, Carey TS, Jennette JC. Clinical course of anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and systemic vasculitis. The Glomerular Disease Collaborative Network. *Ann Intern Med* 1990;**113**:656–663.
18. Crausman RS, Achenbach GA, Pluss WT, O'Brien RF, Jennings CA. Pulmonary capillaritis and alveolar hemorrhage associated with the anti-phospholipid antibody syndrome. *J Rheumatol* 1995;**22**:554–556.
19. Schwarz MI, Sutarik JM, Nick JA, Leff JA, Emlen JW, Tuder RM. Pulmonary capillaritis and diffuse alveolar hemorrhage. A primary manifestation of polymyositis. *Am J Respir Crit Care Med* 1995;**151**:2037–2040.
20. Hughson MD, He Z, Henegar J, McMurray R. Alveolar hemorrhage and renal microangiopathy in systemic lupus erythematosus. *Arch Pathol Lab Med* 2001;**125**:475–483.
21. Erickson RW, Franklin WA, Emlen W. Treatment of hemorrhagic lupus pneumonitis with plasmapheresis. *Semin Arthritis Rheum* 1994;**24**:114–123.
22. Euler HH, Schroeder JO, Harten P, Zeuner RA, Gutschmidt HJ. Treatment-free remission in severe systemic lupus erythematosus following synchronization of plasmapheresis with subsequent pulse cyclophosphamide. *Arthritis Rheum* 1994;**37**:1784–1794.
23. Keane MP, Lynch JP III. Pleuropulmonary manifestations of systemic lupus erythematosus. *Thorax* 2000;**55**:159–166.
24. Specks U. Diffuse alveolar hemorrhage syndromes. *Curr Opin Rheumatol* 2001;**13**:12–17.
25. Fenlon HM, Doran M, Sant SM, Breatnach E. High-resolution chest CT in systemic lupus erythematosus. *AJR Am J Roentgenol* 1996;**166**:301–307.
26. Sant SM, Doran M, Fenlon HM, Breatnach ES. Pleuropulmonary abnormalities in patients with systemic lupus erythematosus: assessment with high resolution computed tomography, chest radiography and pulmonary function tests. *Clin Exp Rheumatol* 1997;**15**:507–513.
27. Eisenberg H, Dubois EL, Sherwin RP, Balchum OJ. Diffuse interstitial lung disease in systemic lupus erythematosus. *Ann Intern Med* 1973;**79**:37–45.
28. Weinrib L, Sharma OP, Quismorio FP Jr. A long-term study of interstitial lung disease in systemic lupus erythematosus. *Semin Arthritis Rheum* 1990;**20**:48–56.
29. Boulware DW, Hedgpeth MT. Lupus pneumonitis and anti-SSA(Ro) antibodies. *J Rheumatol* 1989;**16**:479–481.
30. Groen H, ter Borg EJ, Postma DS, Wouda AA, van der Mark TW, Kallenberg CG. Pulmonary function in systemic lupus erythematosus is related to distinct clinical, serologic, and nail-fold capillary patterns. *Am J Med* 1992;**93**:619–627.
31. Tansey D, Wells AU, Colby TV, Ip S, Nikolakoupolou A, du Bois RM et al. Variations in histological patterns of interstitial pneumonia between connective tissue disorders and their relationship to prognosis. *Histopathology* 2004;**44**:585–596.
32. Fink SD, Kremer JM. Successful treatment of interstitial lung disease in systemic lupus erythematosus with methotrexate. *J Rheumatol* 1995;**22**:967–969.
33. Filipek MS, Thompson ME, Wang PL, Gosselin MV, S LP. Lymphocytic interstitial pneumonitis in a patient with systemic lupus erythematosus: radiographic and high-resolution CT findings. *J Thorac Imaging* 2004;**19**:200–203.
34. Yood RA, Steigman DM, Gill LR. Lymphocytic interstitial pneumonitis in a patient with systemic lupus erythematosus. *Lupus* 1995;**4**:161–163.

35. Yum HK, Kim ES, Ok KS, Lee HK, Choi SJ. Lymphocytic interstitial pneumonitis associated with Epstein-Barr virus in systemic lupus erythematosus and Sjogren's syndrome. Complete remission with corticosteroid and cyclophosphamide. *Korean J Intern Med* 2002;**17**:198-203.
36. Min JK, Hong YS, Park SH, Park JH, Lee SH, Lee YS et al. Bronchiolitis obliterans organizing pneumonia as an initial manifestation in patients with systemic lupus erythematosus. *J Rheumatol* 1997;**24**:2254-2257.
37. Otsuka F, Amano T, Hashimoto N, Takahashi M, Hayakawa N, Makino H et al. Bronchiolitis obliterans organizing pneumonia associated with systemic lupus erythematosus with antiphospholipid antibody. *Intern Med* 1996;**35**:341-344.
38. Gammon RB, Bridges TA, al-Nezir H, Alexander CB, Kennedy JI JR. Bronchiolitis obliterans organizing pneumonia associated with systemic lupus erythematosus. *Chest* 1992;**102**:1171-1174.
39. Loehrl TA, Smith TL. Inflammatory and granulomatous lesions of the larynx and pharynx. *Am J Med* 2001;**111**:113-117.
40. Karim A, Ahmed S, Siddiqui R, Marder GS, Mattana J. Severe upper airway obstruction from cricoarytenoiditis as the sole presenting manifestation of a systemic lupus erythematosus flare. *Chest* 2002;**121**:990-993.
41. Andonopoulos AP, Constantopoulos SH, Galanopoulou V, Drosos AA, Acritidis NC, Moutsopoulos HM. Pulmonary function of nonsmoking patients with systemic lupus erythematosus. *Chest* 1988;**94**:312-315.
42. Perez HD, Kramer N. Pulmonary hypertension in systemic lupus erythematosus: report of four cases and review of the literature. *Semin Arthritis Rheum* 1981;**11**:177-181.
43. Badui E, Garcia-Rubi D, Robles E, Jimenez J, Juan L, Deleze M et al. Cardiovascular manifestations in systemic lupus erythematosus. Prospective study of 100 patients. *Angiology* 1985;**36**:431-441.
44. Simonson JS, Schiller NB, Petri M, Hellmann DB. Pulmonary hypertension in systemic lupus erythematosus. *J Rheumatol* 1989;**16**:918-925.
45. Winslow TM, Ossipov MA, Fazio GP, Simonson JS, Redberg RF, Schiller NB. Five-year follow-up study of the prevalence and progression of pulmonary hypertension in systemic lupus erythematosus. *Am Heart J* 1995;**129**:510-515.
46. Orens JB, Martinez FJ, Lynch JP.III. Pleuropulmonary manifestations of systemic lupus erythematosus. *Rheum Dis Clin North Am* 1994;**20**:159-193.
47. Robbins IM, Gaine SP, Schilz R, Tapson VF, Rubin LJ, Loyd JE. Epoprostenol for treatment of pulmonary hypertension in patients with systemic lupus erythematosus*. *Chest* 2000;**117**:14-18.
48. Kishida Y, Kanai Y, Kuramochi S, Hosoda Y. Pulmonary venoocclusive disease in a patient with systemic lupus erythematosus. *J Rheumatol* 1993;**20**:2161-2162.
49. Resten A, Maitre S, Humbert M, Sitbon O, Capron F, Simoneau G et al. Pulmonary arterial hypertension: thin-section CT predictors of epoprostenol therapy failure. *Radiology* 2002;**222**:782-788.
50. Yoshio T, Masuyama J, Sumiya M, Minota S, Kano S. Antiendothelial cell antibodies and their relation to pulmonary hypertension in systemic lupus erythematosus. *J Rheumatol* 1994;**21**:2058-2063.
51. Humbert M, Sanchez O, Fartoukh M, Jagot JL, Sitbon O, Simonneau G. Treatment of severe pulmonary hypertension secondary to connective tissue diseases with continuous IV epoprostenol (prostacyclin). *Chest* 1998;**114**:80S-82S.
52. Molina J, Lucero E, Luluaga S, Bellomio V, Spindler A, Berman A. Systemic lupus erythematosus-associated pulmonary hypertension: good outcome following sildenafil therapy. *Lupus* 2003;**12**:321-323.
53. Goupille P, Fauchier L, Babuty D, Fauchier JP, Valat JP. Precapillary pulmonary hypertension dramatically improved with high doses of corticosteroids during systemic lupus erythematosus. *J Rheumatol* 1994;**21**:1976-1977.
54. Levine JS, Branch DW, Rauch J. The antiphospholipid syndrome. *N Engl J Med* 2002;**346**:752-763.
55. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. *Medicine (Baltimore)* 1993;**72**:113-124.
56. Asherson RA, Cervera R, Piette JC, Font J, Lie JT, Burcoglu A et al. Catastrophic antiphospholipid syndrome. Clinical and laboratory features of 50 patients. *Medicine (Baltimore)* 1998;**77**:195-207.
57. Wilcox P, Stein H, Clarke S, Pare P, Pardy R. Phrenic nerve function in patients with diaphragmatic weakness and systemic lupus erythematosus. *Chest* 1988;**93**:352-358.
58. Laroche CM, Mulvey DA, Hawkins PN, Walport MJ, Strickland B, Moxham J et al. Diaphragm strength in the shrinking lung syndrome of systemic lupus erythematosus. *Q J Med* 1989;**71**:429-439.
59. Hardy K, Herry I, Attali V, Cadranel J, Similowski T. Bilateral phrenic paralysis in a patient with systemic lupus erythematosus. *Chest* 2001;**119**:1274-1277.
60. Hawkins P, Davison AG, Dasgupta B, Moxham J. Diaphragm strength in acute systemic lupus erythematosus in a patient with paradoxical abdominal motion and reduced lung volumes. *Thorax* 2001;**56**:329-330.
61. Bas S, Perneger TV, Seitz M, Tiercy JM, Roux-Lombard P, Guerne PA. Diagnostic tests for rheumatoid arthritis: comparison of anti-cyclic citrullinated peptide antibodies, anti-keratin antibodies and IgM rheumatoid factors. *Rheumatology* 2002;**41**:809-814.
62. Pettersson T, Soderblom T, Nyberg P, Riska H, Linko L, Klockars M. Pleural fluid soluble interleukin 2 receptor in rheumatoid arthritis and systemic lupus erythematosus. *J Rheumatol* 1994;**21**:1820-1824.
63. Nyberg P, Soderblom T, Pettersson T, Riska H, Klockars M, Linko L. Neurone-specific enolase levels in pleural effusions in patients with rheumatoid arthritis. *Thorax* 1996;**51**:92-94.
64. Lamblin C, Bergoin C, Saelens T, Wallaert B. Interstitial lung diseases in collagen vascular diseases. *Eur Respir J* 2001;**32**:69s-80s.
65. Wisniewski JJ, Askari AD. Rheumatoid nodulosis. A relatively benign rheumatoid variant. *Arch Intern Med* 1981;**141**:615-619.
66. Tanoue LT. Pulmonary manifestations of rheumatoid arthritis. *Clin Chest Med* 1998;**19**:667-685.
67. Dawson JK, Fewins HE, Desmond J, Lynch MP, Graham DR. Fibrosing alveolitis in patients with rheumatoid arthritis as assessed by high resolution computed tomography, chest radiography, and pulmonary function tests. *Thorax* 2001;**56**:622-627.
68. Yousem SA, Colby TV, Carrington CB. Follicular bronchitis/bronchiolitis. *Hum Pathol* 1985;**16**:700-706.
69. Yousem SA, Colby TV, Carrington CB. Lung biopsy in rheumatoid arthritis. *Am Rev Respir Dis* 1985;**131**:770-777.

70. Tanaka N, Kim JS, Newell JD, Brown KK, Cool CD, Meehan R et al. Rheumatoid arthritis-related lung diseases: CT findings. *Radiology* 2004;**232**:81–91.
71. Hakala M. Poor prognosis in patients with rheumatoid arthritis hospitalized for interstitial lung fibrosis. *Chest* 1988;**93**:114–118.
72. Yue CH, Park CH, Kushner I. Apical fibrocavitary lesions of the lung in rheumatoid arthritis. *Am J Med* 1986;**81**:741–746.
73. Cortet B, Flipo RM, Remy-Jardin M, Coquerelle P, Duquesnoy B, Remy J et al. Use of high resolution computed tomography of the lungs in patients with rheumatoid arthritis. *Ann Rheum Dis* 1995;**54**:815–819.
74. McMahon MJ, Swinson DR, Shettar S, Wolstenholme R, Chattopadhyay C, Smith P et al. Bronchiectasis and rheumatoid arthritis: a clinical study. *Ann Rheum Dis* 1993;**52**:776–779.
75. Swinson DR, Symmons D, Suresh U, Jones M, Booth J. Decreased survival in patients with co-existent rheumatoid arthritis and bronchiectasis. *Br J Rheumatol* 1997;**36**:689–691.
76. Suzuki A, Ohosone Y, Obana M, Mita S, Matsuoka Y, Irimajiri S et al. Cause of death in 81 autopsied patients with rheumatoid arthritis. *J Rheumatol* 1994;**21**:33–36.
77. Grennan DM, Gray J, Loudon J, Fear S. Methotrexate and early postoperative complications in patients with rheumatoid arthritis undergoing elective orthopaedic surgery. *Ann Rheum Dis* 2001;**60**:214–217.
78. Snowden N, Moran A, Booth J, Haeney MR, Swinson DR. Defective antibody production in patients with rheumatoid arthritis and bronchiectasis. *Clin Rheumatol* 1999;**18**:132–135.
79. David-Vaudey E, Jamard B, Hermant C, Cantagrel A. Yellow nail syndrome in rheumatoid arthritis: a drug-induced disease? *Clin Rheumatol* 2004;**23**:376–378.
80. Hillarby MC, McMahon MJ, Grennan DM, Cooper RG, Clarkson RW, Davies EJ et al. HLA associations in subjects with rheumatoid arthritis and bronchiectasis but not with other pulmonary complications of rheumatoid disease. *Br J Rheumatol* 1993;**32**:794–797.
81. Puechal X, Fajac I, Bienvenu T, Desmazes-Dufeu N, Hubert D, Kaplan JC et al. Increased frequency of cystic fibrosis deltaF508 mutation in bronchiectasis associated with rheumatoid arthritis. *Eur Respir J* 1999;**13**:1281–1287.
82. Geddes DM, Webley M, Emerson PA. Airways obstruction in rheumatoid arthritis. *Ann Rheum Dis* 1979;**38**:222–225.
83. Vergnenegre A, Pugnere N, Antonini MT, Arnaud M, Melloni B, Treves R et al. Airway obstruction and rheumatoid arthritis. *Eur Respir J* 1997;**10**:1072–1078.
84. Hassan WU, Keaney NP, Holland CD, Kelly CA. Bronchial reactivity and airflow obstruction in rheumatoid arthritis. *Ann Rheum Dis* 1994;**53**:511–514.
85. Homma S, Kawabata M, Kishi K, Tsuboi E, Narui K, Nakatani T et al. Diffuse panbronchiolitis in rheumatoid arthritis. *Eur Respir J* 1998;**12**:444–452.
86. Epler GR, Snider GL, Gaensler EA, Cathcart ES, FitzGerald MX, Carrington CB. Bronchiolitis and bronchitis in connective tissue disease. A possible relationship to the use of penicillamine. *JAMA* 1979;**242**:528–532.
87. Pegg SJ, Lang BA, Mikhail EL, Hughes DM. Fatal bronchiolitis obliterans in a patient with juvenile rheumatoid arthritis receiving chrysotherapy. *J Rheumatol* 1994;**21**:549–551.
88. Lofgren RH, Montgomery WW. Incidence of laryngeal involvement in rheumatoid arthritis. *N Engl J Med* 1962;**267**:193–195.
89. Bayar N, Kara SA, Keles I, Koc C, Altinok D, Orkun S. Cricoarytenoiditis in rheumatoid arthritis: radiologic and clinical study. *J Otolaryngol* 2003;**32**:373–378.
90. Dawson JK, Goodson NG, Graham DR, Lynch MP. Raised pulmonary artery pressures measured with Doppler echocardiography in rheumatoid arthritis patients. *Rheumatology* 2000;**39**:1320–1325.
91. Naschitz JE, Yeshurun D, Scharf Y, Sajrawi I, Lazarov NB, Boss JH. Recurrent massive alveolar hemorrhage, crescentic glomerulonephritis, and necrotizing vasculitis in a patient with rheumatoid arthritis. *Arch Intern Med* 1989;**149**:406–408.
92. Torralbo A, Herrero JA, Portoles J, Barrientos A. Alveolar hemorrhage associated with antineutrophil cytoplasmic antibodies in rheumatoid arthritis. *Chest* 1994;**105**:1590–1592.
93. Libby D, White DA. Pulmonary toxicity of drugs used to treat systemic autoimmune diseases. *Clin Chest Med* 1998;**19**:809–821.
94. Camus P, Foucher P, Bonniaud P, Ask K. Drug-induced infiltrative lung disease. *Eur Respir J* 2001;**18**:93s–100s.
95. Foucher P, Camus P. Pneumotox on the web. <http://www.pneumotox.com>.
96. Cain HC, Noble PW, Matthay RA. Pulmonary manifestations of Sjögren's syndrome. *Clin Chest Med* 1998;**19**:687–699.
97. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE et al. Classification criteria for Sjögren's Syndrome: a revised version of the European criteria proposed by the American-European consensus group. *Ann Rheum Dis* 2002;**61**:554–558.
98. Deheinzeln D, Capelozzi VL, Kairalla RA, Barbas Filho JV, Nascimento Saldiva PH, Ribeiro de Carvalho CR. Interstitial lung disease in primary Sjögren's Syndrome: clinical pathological evaluation and response to treatment. *Am J Respir Crit Care Med* 1996;**154**:794–799.
99. Franquet T, Giménez A, Monill JM, Diaz C, Geli C. Primary Sjögren's Syndrome and associated lung disease: CT findings in 50 patients. *AJR* 1997;**169**:655–658.
100. Constantopoulos SH, Papadimitriou CS, Moutsopoulos MH. Respiratory manifestations in primary Sjögren's Syndrome: a clinical, functional, and histologic study. *Chest* 1985;**88**:226–229.
101. Strimlan CV, Rosenow EC, Divertie MB, Harrison EG. Pulmonary manifestations of Sjögren's Syndrome. *Chest* 1976;**70**:354–361.
102. Davidson BKS, Kelly CA, Griffiths ID. Ten year of follow up of pulmonary function in patients with primary Sjögren's Syndrome. *Ann Rheum Dis* 2000;**59**:709–712.
103. Ryu JH, Myers JL, Swensen SJ. Bronchiolar disorders. *Am J Respir Crit Care Med* 2003;**168**:1277–1292.
104. Papisis SA, Saetta M, Turato G, La Corte R, Trevisani L, Mapp CE et al. CD4-positive T-lymphocytes infiltrate the bronchial mucosa of patients with Sjögren's Syndrome. *Am J Respir Crit Care Med* 1997;**156**:637–641.
105. Mialon P, Barthélémy L, Sebert P, Le Hénaff C, Sarni D, Penneç YL et al. A longitudinal study of lung impairment in patients with primary Sjögren's Syndrome. *Clin Exp Rheumatol* 1997;**15**:349–354.
106. Papathanasiou MP, Constantopoulos SH, Tsampoulas C, Drosos AA, Moutsopoulos HM. Reappraisal of respiratory abnormalities in primary and secondary Sjögren's Syndrome. *Chest* 1986;**90**:370–374.

107. Gudbjörnsson B, Hedenström H, Stalenheim G, Hällgren R. Bronchial hyperresponsiveness to methacholine in patients with primary Sjögren's Syndrome. *Ann Rheum Dis* 1991;**50**:36–40.
108. Stalenheim G, Gudbjörnsson B. Anti-inflammatory drugs do not alleviate bronchial hyperreactivity in Sjögren's syndrome. *Allergy* 1997;**52**:423–427.
109. Papisir A, Maniati M, Constantopoulos SH, Roussos C, Moustopoulos HM, Skopouli FN. Lung involvement in primary Sjögren's Syndrome is mainly related to the small airway disease. *Ann Rheum Dis* 1999;**58**:61–64.
110. Uffman M, Kiener HP, Bankier AA, Baldt MM, Zontsich T, Herold CJ. Lung manifestation in asymptomatic patients with primary Sjögren's Syndrome: assessment with high resolution CT and pulmonary function tests. *J Thorac Imaging* 2001;**16**:282–289.
111. Koyama M, Johkoh T, Honda O, Mihara N, Kozuka T, Tomiyama N et al. Pulmonary involvement in primary Sjögren's Syndrome: spectrum of pulmonary abnormalities and computed tomography findings in 60 patients. *J Thorac Imaging* 2001;**16**:290–296.
112. Taouli B, Brauner M, Mourey I, Lemouchi D, Grenier P. Thin-section chest CT findings of primary Sjögren's Syndrome: correlation with pulmonary function. *Eur Radiol* 2002;**1**:1504–1511.
113. Yamadori I, Fujita J, Bandoh S, Tokuda M, Tanimoto Y, Kataoka M et al. Nonspecific interstitial pneumonia as pulmonary involvement of primary Sjögren's syndrome. *Rheumatol Int* 2002;**22**:89–92.
114. Johkoh T, Ichikado K, Akira M, Honda O, Tomiyama N, Mihara N et al. Lymphocytic interstitial pneumonia: follow-up CT findings in 14 patients. *J Thorac Imaging* 2000;**15**:162–167.
115. Hatron PY, Wallaert B, Gosset D, Tonnel AB, Gosselin B, Voisin C et al. Subclinical lung inflammation in primary Sjögren's syndrome. Relationship between bronchoalveolar lavage cellular analysis findings and characteristics of the disease. *Arthritis Rheum* 1987;**30**:1226–1231.
116. Wallaert B, Prin L, Hatron PY, Ramon P, Tonnel AB, Voisin C. Lymphocyte subpopulations in bronchoalveolar lavage in Sjögren's syndrome. Evidence for an expansion of cytotoxic/suppressor subset in patients with alveolar neutrophilia. *Chest* 1987;**92**:1025–1031.
117. Wallaert B, Hatron PY, Grosbois JM, Tonnel AB, Devulder B, Voisin C. Subclinical pulmonary involvement in collagen-vascular diseases assessed by bronchoalveolar lavage. *Am Rev Respir Dis* 1986;**133**:574–580.
118. Linstow M, Kriegbaum NJ, Backer V, Ulrik C, Oxholm P. A follow-up study of pulmonary function in patients with primary Sjögren's syndrome. *Rheumatol Int* 1990;**10**:47–49.
119. Salaffi F, Manganelli P, Carotti M, Baldelli S, Blasetti P, Subiaco S et al. A longitudinal study of pulmonary involvement in primary Sjögren's syndrome: relationship between alveolitis and subsequent lung changes on high-resolution computed tomography. *Br J Rheumatol* 1998;**37**:263–269.
120. Fox RI. Sjögren's syndrome: evolving therapies. *Expert Opin Investig Drugs* 2003;**12**:247–254.
121. Hansen LA, Prakash UB, Colby TV. Pulmonary lymphoma in Sjögren's syndrome. *Mayo Clin Proc* 1989;**64**:920–931.
122. Royer B, Cazals-Hatem D, Sibilia J, Agbalika F, Cayuela JM, Soussi T et al. Lymphomas in patients with Sjögren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites, and are not associated with viruses. *Blood* 1997;**90**:766–775.
123. Cordier JF, Chailleux E, Lauque D, Reynaud-Gaubert M, Dietemann-Molard A, Dalphin JC et al. Primary pulmonary lymphomas. A clinical study of 70 cases in nonimmunocompromised patients. *Chest* 1993;**103**:201–208.
124. Isaacson PG, Du MQ. MALT lymphoma: from morphology to molecules. *Nat Rev Cancer* 2004;**4**:644–653.
125. Mariette X, Brenot F, Brouet J-C. Recovery from pulmonary hypertension with steroid therapy in a patient with Sjögren's Syndrome and polymyositis. *J Rheumatol* 1994;**21**:772–773.
126. Radenne F, Tillie-Leblond I, Muraige CA, Rémy-Jardin M, Wallaert B, Tonnel AB. Gougerot-Sjögren et granulomatose nécrosante sarcoïdique. *Rev Mal Respir* 1999;**16**:554–557.
127. Altman RD, Medsger TA Jr, Bloch DA, Michel BA. Predictors of survival in systemic sclerosis (scleroderma). *Arthritis Rheum* 1991;**34**:403–413.
128. Minai OA, Dweik RA, Arroliga AC. Manifestations of scleroderma pulmonary disease. *Clin Chest Med* 1998;**19**:713–731.
129. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988;**15**:202–205.
130. Ferri C, Valentini G, Cozzi F, Sebastiani M, Michelassi C, La Montagna G et al. Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. *Medicine (Baltimore)* 2002;**81**:139–153.
131. Lomeo RM, Cornella RJ, Schabel SI, Silver RM. Progressive systemic sclerosis sine scleroderma presenting as pulmonary interstitial fibrosis. *Am J Med* 1989;**87**:525–527.
132. Steen VD, Conte C, Owens GR, Medsger TA Jr. Severe restrictive lung disease in systemic sclerosis. *Arthritis Rheum* 1994;**37**:1283–1289.
133. Wells AU, Cullinan P, Hansell DM, Rubens MB, Black CM, Newman-Taylor AJ et al. Fibrosing alveolitis associated with systemic sclerosis has a better prognosis than lone cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med* 1994;**149**:1583–1590.
134. Fujita J, Yoshinouchi T, Ohtsuki Y, Tokuda M, Yang Y, Yamadori I et al. Non-specific interstitial pneumonia as pulmonary involvement of systemic sclerosis. *Ann Rheum Dis* 2001;**60**:281–283.
135. Kim DS, Yoo B, Lee JS, Kim EK, Lim CM, Lee SD et al. The major histopathologic pattern of pulmonary fibrosis in scleroderma is nonspecific interstitial pneumonia. *Sarcoidosis Vasc Diffuse Lung Dis* 2002;**19**:121–127.
136. Bouros D, Wells AU, Nicholson AG, Colby TV, Polychronopoulos V, Pantelidis P et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. *Am J Respir Crit Care Med* 2002;**165**:1581–1586.
137. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med* 2000;**161**:646–664.
138. Latsi PI, Wells AU. Evaluation and management of alveolitis and interstitial lung disease in scleroderma. *Curr Opin Rheumatol* 2003;**15**:748–755.
139. Wells AU, Hansell DM, Corrin B, Harrison NK, Goldstraw P, Black CM et al. High resolution computed tomography as a predictor of lung histology in systemic sclerosis. *Thorax* 1992;**47**:738–742.
140. MacDonald SLS, Rubens MB, Hansell DM, Copley SJ, Desai SR, du Bois RM et al. Nonspecific interstitial pneumonia and usual interstitial pneumonia: comparative appearances at and diagnostic accuracy of thin-section CT. *Radiology* 2001;**221**:600–605.

141. Silver RM, Miller KS, Kinsella M, Smith EA, Schabel SI. Evaluation and management of scleroderma lung disease using bronchoalveolar lavage. *Am J Med* 1990;**88**:470–476.
142. Behr J, Vogelmeier C, Beinert T, Meurer M, Krombach F, König G et al. Bronchoalveolar lavage for evaluation and management of scleroderma disease of the lung. *Am J Respir Crit Care Med* 1996;**154**:400–406.
143. White B, Moore WC, Wigley FM, Xiao HQ, Wise RA. Cyclophosphamide is associated with pulmonary function and survival benefit in patients with scleroderma and alveolitis. *Ann Intern Med* 2000;**132**:947–954.
144. Pakas I, Ioannidis JP, Malagari K, Skopouli FN, Moutsopoulos HM, Vlachoyiannopoulos PG. Cyclophosphamide with low or high dose prednisolone for systemic sclerosis lung disease. *J Rheumatol* 2002;**29**:298–304.
145. Giacomelli R, Valentini G, Salsano F, Cipriani P, Sambo P, Conforti ML et al. Cyclophosphamide pulse regimen in the treatment of alveolitis in systemic sclerosis. *J Rheumatol* 2002;**29**:731–736.
146. Griffiths B, Miles S, Moss H, Robertson R, Veale D, Emery P. Systemic sclerosis and interstitial lung disease: a pilot study using pulse intravenous methylprednisolone and cyclophosphamide to assess the effect on high resolution computed tomography scan and lung function. *J Rheumatol* 2002;**29**:2371–2378.
147. Clements PJ, Lachenbruch PA, Sterz M, Danovitch G, Hawkins R, Ippoliti A et al. Cyclosporine in systemic sclerosis. Results of a forty-eight-week open safety study in ten patients. *Arthritis Rheum* 1993;**36**:75–83.
148. Clements PJ, Furst DE, Wong WK, Mayes M, White B, Wigley F et al. High-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis: analysis of a two-year, double-blind, randomized, controlled clinical trial. *Arthritis Rheum* 1999;**42**:1194–1203.
149. Farge D, Passweg J, van Laar JM, Marjanovic Z, Besenthal C, Finke J et al. Autologous stem cell transplantation in the treatment of systemic sclerosis: report from the EBMT/EULAR Registry. *Ann Rheum Dis* 2004;**63**:974–981.
150. Stupi AM, Steen VD, Owens GR, Barnes EL, Rodnan GP, Medsger TA Jr. Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. *Arthritis Rheum* 1986;**29**:515–524.
151. Cool CD, Kennedy D, Voelkel NF, Tuder RM. Pathogenesis and evolution of plexiform lesions in pulmonary hypertension associated with scleroderma and human immunodeficiency virus infection. *Hum Pathol* 1997;**28**:434–442.
152. Dorfmueller P, Perros F, Balabanian K, Humbert M. Inflammation in pulmonary hypertension. *Eur Respir J* 2003;**22**:358–363.
153. Mukerjee D, St George D, Coleiro B, Knight C, Denton CP, Davar J et al. Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Ann Rheum Dis* 2003;**62**:1088–1093.
154. Mukerjee D, St George D, Knight C, Davar J, Wells AU, Du Bois RM et al. Echocardiography and pulmonary function as screening tests for pulmonary arterial hypertension in systemic sclerosis. *Rheumatology* 2004;**43**:461–466.
155. Alpert MA, Pressly TA, Mukerji V, Lambert CR, Mukerji B, Panayiotou H et al. Acute and long-term effects of nifedipine on pulmonary and systemic hemodynamics in patients with pulmonary hypertension associated with diffuse systemic sclerosis, the CREST syndrome and mixed connective tissue disease. *Am J Cardiol* 1991;**68**:1687–1691.
156. Badesch DB, McLaughlin VV, Delcroix M, Vizza CD, Olschewski H, Sitbon O et al. Prostanoid therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2004;**43**:56S–61S.
157. Sanchez O, Humbert M, Sitbon O, Nunes H, Garcia G, Simonneau G. Pulmonary hypertension associated with connective tissue diseases. *Rev Med Interne* 2002;**23**:41–54.
158. Gugnani MK, Pierson C, Vanderheide R, Girgis RE. Pulmonary edema complicating prostacyclin therapy in pulmonary hypertension associated with scleroderma: a case of pulmonary capillary hemangiomatosis. *Arthritis Rheum* 2000;**43**:699–703.
159. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;**346**:896–903.
160. Humbert M, Cabane J. Successful treatment of systemic sclerosis digital ulcers and pulmonary arterial hypertension with endothelin receptor antagonist bosentan. *Rheumatology* 2003;**42**:191–193.
161. Rosenkranz S, Diet F, Karasch T, Wehrauch J, Wassermann K, Erdmann E. Sildenafil improved pulmonary hypertension and peripheral blood flow in a patient with scleroderma-associated lung fibrosis and the raynaud phenomenon. *Ann Intern Med* 2003;**139**:871–873.
162. Rosas V, Conte JV, Yang SC, Gaine SP, Borja M, Wigley FM et al. Lung transplantation and systemic sclerosis. *Ann Transplant* 2000;**5**:38–43.
163. Abu-shakra M, Guillemin F, Lee P. Cancer in systemic sclerosis. *Arthritis Rheum* 1993;**36**:460–464.
164. Hill CL, Nguyen AM, Roder D, Roberts-Thomson P. Risk of cancer in patients with scleroderma: a population based cohort study. *Ann Rheum Dis* 2003;**62**:728–731.
165. Yang Y, Fujita J, Tokuda M, Bandoh S, Ishida T. Chronological evaluation of the onset of histologically confirmed interstitial pneumonia associated with polymyositis/dermatomyositis. *Intern Med* 2002;**41**:1135–1141.
166. Imbert-Masseau A, Hamidou M, Agard C, Grolleau JY, Cherin P. Antisynthetase syndrome. *Joint Bone Spine* 2003;**70**:161–168.
167. Sauty A, Rochat T, Schoch OD, Hamacher J, Kurt AM, Dayer JM et al. Pulmonary fibrosis with predominant CD8 lymphocytic alveolitis and anti-Jo-1 antibodies. *Eur Respir J* 1997;**10**:2907–2912.
168. Dauriat G, Stern JB, Similowski T, Herson S, Belmatoug N, Marceau A et al. Acute respiratory failure due to diaphragmatic weakness revealing a polymyositis. *Eur J Intern Med* 2002;**13**:203–205.
169. Grateau G, Roux ME, Franck N, Bachmeyer C, Taulera O, Forest M et al. Pulmonary hypertension in a case of dermatomyositis. *J Rheumatol* 1993;**20**:1452–1453.
170. Marie I, Hatron PY, Levesque H, Hachulla E, Hellot MF, Michon-Pasturel U, et al. Influence of age on characteristics of polymyositis and dermatomyositis in adults. *Medicine (Baltimore)* 1999;**78**:139–147.
171. Marie I, Hachulla E, Hatron PY, Hellot MF, Levesque H, Devulder B et al. Polymyositis and dermatomyositis: short term and longterm outcome, and predictive factors of prognosis. *J Rheumatol* 2001;**28**:2230–2237.
172. Douglas WW, Tazelaar HD, Hartman TE, Hartman RP, Decker PA, Schroeder DR et al. Polymyositis-dermatomyositis-associated interstitial lung disease. *Am J Respir Crit Care Med* 2001;**164**:1182–1185.

173. Marie I, Hachulla E, Cherin P, Dominique S, Hatron PY, Hellot MF et al. Interstitial lung disease in polymyositis and dermatomyositis. *Arthritis Rheum* 2002;**47**:614–622.
174. Cottin V, Thivolet-Bejui F, Reynaud-Gaubert M, Cadranel J, Delaval P, Ternamian PJ et al. Interstitial lung disease in amyopathic dermatomyositis, dermatomyositis and polymyositis. *Eur Respir J* 2003;**22**:245–250.
175. Evans J. Antinuclear antibody testing in systemic autoimmune disease. *Clin Chest Med* 1998;**19**:613–625.
176. Fathi M, Dastmalchi M, Rasmussen E, Lundberg IE, Tornling G. Interstitial lung disease, a common manifestation of newly diagnosed polymyositis and dermatomyositis. *Ann Rheum Dis* 2004;**63**:297–301.
177. Lee CS, Chen TL, Tzen CY, Lin FJ, Peng MJ, Wu CL et al. Idiopathic inflammatory myopathy with diffuse alveolar damage. *Clin Rheumatol* 2002;**21**:391–396.
178. Fata F, Rathore R, Schiff C, Herzlich BC. Bronchiolitis obliterans organizing pneumonia as the first manifestation of polymyositis. *South Med J* 1997;**90**:227–230.
179. Arakawa H, Yamada H, Kurihara Y, Nakajima Y, Takeda A, Fukushima Y et al. Nonspecific interstitial pneumonia associated with polymyositis and dermatomyositis: serial high-resolution CT findings and functional correlation. *Chest* 2003;**123**:1096–1103.
180. Bonnefoy O, Ferretti G, Calaque O, Coulomb M, Begueret H, Beylot-Barry M et al. Serial chest CT findings in interstitial lung disease associated with polymyositis-dermatomyositis. *Eur J Radiol* 2004;**49**:235–244.
181. Schnabel A, Reuter M, Biederer J, Richter C, Gross WL. Interstitial lung disease in polymyositis and dermatomyositis: clinical course and response to treatment. *Semin Arthritis Rheum* 2003;**32**:273–284.
182. Oddis CV, Sciruba FC, Elmagd KA, Starzl TE. Tacrolimus in refractory polymyositis with interstitial lung disease. *Lancet* 1999;**353**:1762–1763.
183. Cherin P, Pelletier S, Teixeira A, Laforet P, Genereau T, Simon A et al. Results and long-term followup of intravenous immunoglobulin infusions in chronic, refractory polymyositis: an open study with thirty-five adult patients. *Arthritis Rheum* 2002;**46**:467–474.
184. Hill CL, Zhang Y, Sigurgeirsson B, Pukkala E, Mellekjaer L, Airio A et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. *Lancet* 2001;**357**:96–100.
185. Prakash UB. Respiratory complications in mixed connective tissue disease. *Clin Chest Med* 1998;**19**:733–746.