REVIEW

Interstitial lung diseases in collagen vascular diseases

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Interstitial lung diseases in collagen vascular diseases. C. Lamblin, C. Bergoin, T. Saelens, B. Wallaert. ©ERS Journals Ltd 2001.
ABSTRACT: In this review, a clinical update is presented of the most important collagen vascular diseases (CVDs) and the different types of interstitial lung disease (ILD) encountered in these CVDs. These CVDs represent a heterogenous group of immunologically mediated inflammatory disorders with a large variety of affected organs besides the lungs.

The frequency, clinical presentation, prognosis and response to therapy vary depending on the histological pattern (usual interstitial pneumonia, desquamative interstitial pneumonia, organising pneumonia, diffuse alveolar damage, nodular lesions, *etc.*), as well as on the underlying CVD (scleroderma, rheumatoid arthritis, systemic lupus erythematosus, dermatopolymyositis, Sjögren's syndrome or mixed connective tissue disease).

The diagnosis of most of these CVDs is based on a number of criteria; in several of these, however, lung involvement is not part of the diagnostic criteria. In addition, there may be overlaps between several of these CVDs.

Optimal treatment varies depending on the type of collagen vascular disease and the presence of interstitial lung disease, although in many cases, a combination of corticosteroids and cytostatic drugs are given.
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Collagen vascular diseases (CVDs) represent an heterogenous group of immunologically mediated inflammatory disorders. As a result of the inflammatory reaction a large variety of organs may be affected. Pulmonary involvement is frequent in the course of rheumatological diseases, and may be due to various causes including infection, drug toxicity and specific manifestations of the immune process [1, 2]. This paper will focus on interstitial lung diseases (ILD) associated with CVD excluding other types of lung involvement such as pulmonary vascular disease, bronchiolitis, and other airspace abnormalities.

Scleroderma

Interstitial lung disease

Clinical features. Interstitial lung disease (ILD) is the most common feature in scleroderma. ILD may occur in either limited or diffuse cutaneous scleroderma. Up to 70–80% of patients exhibit pathological abnormalities of pulmonary fibrosis at autopsy [3–5]. Rapid onset of pulmonary fibrosis is rare, pulmonary symptoms rarely precede scleroderma and the vast majority of patients exhibit gradually progressive symptoms during the course of scleroderma. Dyspnoea upon exertion and nonproductive cough are the most common manifestations of pulmonary fibrosis. Nevertheless dyspnoea may be present in patients without radiological or physiological evidence of pulmonary fibrosis, suggesting the presence of pulmonary vascular

disease. On physical examination, the most common abnormality is the presence of bibasal dry "velcro" crackles. Pulmonary fibrosis preferentially occurs at the lung bases and progressively expands to involve the lower two-thirds of the lungs (fig. 1). The incidence
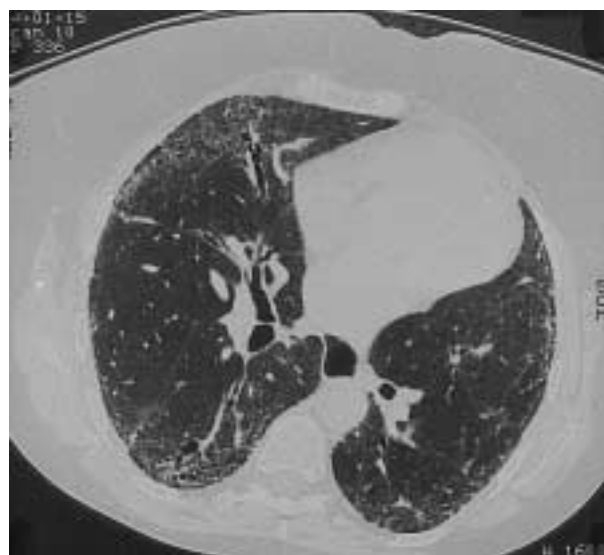

Fig. 1.–Scleroderma. High-resolution computed tomography shows a bilateral microscopic honeycomb pattern with a predominant distribution in the peripheral lung zones compatible with lung fibrosis secondary to scleroderma. Note the characteristically dilated oesophagus.

of radiographically detectable ILD varies from 25–65%; in addition recent studies using high-resolution computed tomography (HRCT) demonstrated that many patients with normal chest radiography had HRCT evidence of ILD [6, 7].

Physiological studies have shown a restrictive pattern with a decreased total lung capacity (TLC), vital capacity (VC) and/or forced vital capacity (FVC) and impairment of the transfer factor (or diffusing capacity) for carbon monoxide (TL,CO). Occult pulmonary impairment may be present in patients with normal pulmonary function tests (PFTs) which may be demonstrated by cardiorespiratory exercise testing [8]. With progression of the ILD, the restrictive pattern is paralleled by the decrease in gas exchange. As demonstrated by WELLS et al. [9], TL,CO is the best index of the extent of the ILD when compared with HRCT as the "gold standard". Interestingly, patients with ILD-scleroderma have a better survival rate (86% at 5 yrs) than patients with idiopathic pulmonary fibrosis (IPF) (50% at 5 yrs) [10].

Serum antitopoisomerase (Scl-70) correlates with the development of ILD and is more frequently found in patients with diffuse cutaneous involvement; anti-centromere antibody is more frequently associated with limited cutaneous scleroderma and pulmonary vascular disease.

Pathology. The scleroderma pulmonary fibrosis is morphologically indistinguishable from IPF. Early changes include interstitial oedema and widening and inflammation of the alveolar walls with collections of mononuclear cells and neutrophils, leading to a combination of an inflammatory reaction and concommittant fibroblast proliferation [11, 12]. Although large cystic airspaces can be observed within areas of lung fibrosis, the most typical feature is the presence of numerous tiny cysts resulting from progressive thinning and rupture of the alveolar walls associated with extensive interstitial fibrosis and peribronchial fibrosis [13]. Pulmonary hypertension, secondary to the underlying fibrotic changes occurring in the lung parenchyma, may be present, although isolated pulmonary hypertension, secondary to vascular changes, may be observed, leading to various degrees of luminal occlusion, independently of the degree of interstitial fibrosis [14, 15]. More recently, retrospective studies of lung biopsies in patients with ILD-scleroderma suggest that the pathological pattern of lung involvement was more frequently that of nonspecific interstitial pneumonia (NSIP) than of usual interstitial pneumonia (UIP) [16].

Pathophysiology. The pathogenesis of scleroderma lung disease is poorly understood. Recent research on pulmonary involvement in scleroderma largely emphasizes two theories: the vascular and the immunologically-mediated inflammatory theories, although these factors probably act together to induce pulmonary fibrosis.

The mechanisms for pulmonary capillary endothelial injury are unknown. Autoantibodies directed against endothelial cells have been demonstrated in scleroderma (as in other autoimmune diseases) but the relationship with endothelial activation and/or injury has not been established [17–19]. Indeed, pathogenesis of the vascular lesion may have a multifactorial basis. Early in the course of scleroderma, activated fibroblasts expressing high levels of type I and type III collagen messenger ribonucleic acid (mRNA) are present adjacent to blood vessels, suggesting the occurence of a vascular-related event mediating both fibroblast activation and tissue fibrosis [20]. Increased levels of endothelin-1, a vasoconstrictor and mitogenic peptide, which is believed to play a role in fibrosis and collagen production, has been found in the plasma of scleroderma patients [19] and in the lungs of patients with IPF [21]. These data suggest an increased expression and/or production of endothelin by the vascular endothelium in scleroderma, which might be mediated, at least in part, by cytokines (tumour necrosis factor (TNF)-α, transforming growth factor (TGF)-β, interleukin (IL)-8) released from alveolar inflammarory cells. In addition, intense expression of platelet derived growth factor (PDGF) by the endothelial lining of small capillaries in scleroderma [22] suggests that endothelin may act in synergy with other cytokines and growth factors to activate fibroblasts.

Consistent with the concept that immune processes initiate the inflammatory process, immune complexes are found in the epithelial lining fluid of patients with scleroderma [23, 24]. Several lines of evidence support the concept that alveolitis, *i.e.* the accumulation of immune and inflammatory cells within the alveolar structures, precedes lung injury and may be the first step of the fibrotic process for which it may be entirely responsible. The alveolitis in scleroderma is characterized by an accumulation of activated alveolar macrophages, lymphocytes, neutrophils and eosinophils [11, 25–32]. Scleroderma patients with ILD have a greater proportion of neutrophils and eosinophils than controls; they are also younger than patients without ILD and tend to have a shorter duration of illness. Bronchoalveolar lavage (BAL) lymphocytosis appeared most often in patients before or soon after the onset of pulmonary symptoms [31]. In addition, BAL abnormalities were also observed in the lower respiratory tract of patients with scleroderma, but without obvious pulmonary involvement, the so-called subclinical inflammatory alveolitis [33, 34], suggesting again that inflammatory changes might be the first step leading towards pulmonary fibrosis rather than a secondary process.

Conceptually, the inflammatory process can damage both the lung cellular and extracellular matrix and initiate the repair mechanisms. Inflammatory cells, especially neutrophils and eosinophils are capable of damaging the normal structures of the lung by releasing reactive oxidant species and proteolytic enzymes. In scleroderma, alveolar macrophages have been shown to spontaneously release greater amounts of superoxide anion than normal alveolar macrophages [27]. Collagenase, neutrophil elastase and elastase-like activities have been found in BAL fluid [28, 35]. Inflammatory cells can also activate the coagulation system (increased levels of plasminogen activator are present in BAL fluid) [36]

and release various mediators leading to the recruitment and accumulation of fibroblasts, and to the formation of connective tissue matrix substances. Alveolar macrophages from scleroderma patients release exaggerated amounts of IL-1, IL-6, TNF-α, fibronectin and alveolar macrophage derived growth factor [26, 29, 30, 37]. Cytokines induce the recruitment of inflammatory cells by the induction of chemokines [38] or by the modulation of cellular adhesion molecule expression by vascular endothelium and leukocytes [39, 40]. In this context, CARRÉ et al. [41] recently demonstrated increased expression of IL-8 mRNA and IL-8 protein by alveolar macrophages from patients with ILD associated with scleroderma. The presence of high levels of IL-8 in BAL fluid correlates with the percentage of neutrophils [42]. Moreover, monokines are known either to stimulate fibroblast growth directly or through induction of growth factors potentially active in fibroblast proliferation [43], or to inhibit fibroblast growth through prostaglandin E2 (PGE$_2$) synthesis. The fibrogenic TGF-β and PDGF are elevated in BAL fluid [44]. Thus, particular reactivity of fibroblasts in the scleroderma lung may result from the result of the opposing effects of inhibitory and stimulatory cytokines [45].

The role of mast cells and their possible cooperation with fibroblasts in the scleroderma lung has been stressed [46]. Masts cells have been described in close contact with interstitial fibroblasts in the scleroderma lung [12]. Interestingly, the percentage of mast cells and the levels of histamine and tryptase were higher in scleroderma patients with pulmonary fibrosis than in patients without obvious pulmonary fibrosis.

All these findings support the hypothesis that inflammatory and immune effector cells might modulate the injury and repair process occurring in the lung of scleroderma patients.

Management. There is still no convincing evidence that the evaluation of the inflammation by BAL will help to better manage the pulmonary fibrosis associated with scleroderma [47]. However, based on the concept that persistent alveolitis is associated with a significant reduction of lung volumes and TL,CO, several anti-inflammatory drugs have been used in the treatment of established scleroderma lung fibrosis. Although corticosteroids have no apparent effect in the treatment of pulmonary fibrosis, when used at an early stage of the disease, they improve pulmonary function [33] and alveolitis [30]. Colchicine has been shown to suppress the release of fibroblast growth factors from alveolar macrophages *in vitro* [48], but does not demonstrate significant efficiency in scleroderma. D-Penicillamine, an immunosuppressive agent that inhibits collagen synthesis and maturation, has been shown to stabilize or even improve the TL,CO, but not the FVC [49, 50]. However, neither study was controlled and one even had a retrospective design. Other immunosuppressive drugs tried in scleroderma include chlorambucil and cyclophosphamide. While chlorambucil did not induce significant improvement [51], cyclophosphamide has provided the most promising evidence for successful treatment of the alveolitis [52]. Either pulse or oral cyclophosphamide therapy is effective in suppressing active alveolitis (ground glass appearance on HRCT) and may improve the outcome of scleroderma patients [53]. A preliminary study did not demonstrate efficacy of cyclosporine A on pulmonary parameters, whereas skin thickness was decreased [54]. Single lung transplantation has been performed in a few patients with scleroderma and terminal lung fibrosis; this procedure was later complicated by problems due to persistent gastroesophageal reflux.

Diffuse alveolar damage

Diffuse alveolar damage (DAD) is a relatively nonspecific pattern of acute lung injury that has been recently described in patients with scleroderma [55].

Rheumatoid arthritis

Interstitial lung disease

Clinical features. Following its description by ELLMANN and BALL [56], ILD quickly appeared as the predominant pulmonary manifestation of rheumatoid arthritis (RA) (after excluding drug-induced pulmonary disease) [57]. Initial radiographical studies found a low incidence of 1.6–5% of ILD in RA [58]. Systematic PFTs detected a decreased diffusing capacity in 41% of patients, and among them, 50% exhibited features of fibrosis associated with lymphoid infiltrates in lung biopsy [59]. Furthermore lung biopsy performed in a group of unselected patients demonstrated interstitial lesions in 80% of cases, among which nearly half were asymptomatic [60]. Prevalence of pleuropulmonary manifestations is clearly increased in males and in smokers [61, 62]. Coexisting subcutaneous rheumatoid nodules, high titres of circulating rheumatoid factor or antinuclear antibodies are also considered significant risk factors [63] while the incidence of ILD appears unrelated to the severity of articular disease.

Genetic factors have also been described. Relative risk of ILD is markedly increased in patients with non-M1M1 α_1-antitrypsin phenotypes [64, 65]. Arthritis precedes the development of ILD in ~90% of affected patients. Mean age at lung disease onset is the fifth or sixth decade.

Clinical manifestations are nonspecific, with progressive exertional dyspnoea and nonproductive cough as the most common symptoms. However, dyspnoea may appear late in the course of the disease, since polyarthritis often severely reduces physical activity in these patients. Clinical examination demonstrates fine bibasal coarse crackles in most patients. Clubbing is less common than in patients with IPF.

Radiographical abnormalities are also indistinguishable from ILD caused by other diseases. The chest radiograph may be normal in patients with early fibrosis. Early acinar pattern is followed by nodular-reticular infiltrates, with a lower lobe predominance as a rule. Progression to end-stage fibrosis results in the

classical honeycombing pattern. Coexisting pleural effusion is common. There is no correlation between the severity of radiographical infiltrates and histological data [66]. HRCT is much more sensitive than plain chest radiography in the assessment of ILD and its higher sensitivity should allow an earlier diagnosis, as is also the case in IPF and scleroderma. The coexistence of airway thickening and dilatation outside the fibrotic area is also highly suggestive of RA. HRCT shows similar lesions, including ground glass opacification, basal honeycombing, traction bronchiectasis and emphysema (fig. 2) [67–69]. HRCT was able to detect interstitial pneumonitis in 17/29 RA patients with a normal chest radiography [70]. HRCT should, therefore, be performed in all RA patients presenting with either risk factors for ILD or minor changes on chest radiographs.

Pathology. Histological findings in RA-related ILDs are classically indistinguishable from other diseases, including IPF. Lesions appear to run a continuum from early cellular infiltrates to end-stage fibrosis with honeycombing. The wide spectrum of elementary lesions found in a series of 40 patients led to the determination in each patient of a predominant or primary pattern [66]. UIP was the most frequent lesion, followed by peribronchovascular and interlobular lymphoid hyperplasia. Cellular interstitial pneumonia and desquamative interstitial pneumonia (DIP) were the primary pattern in six cases. Immunofluorescent studies inconsistent found deposits of immunoglobulins and rheumatoid factors. Proliferative bronchiolitis with patchy organizing pneumonia was also common, as will be discussed further. Constrictive bronchiolitis is another pattern of bronchiolar involvement, which was first described by GEDDES *et al.* [64] in 5 RA patients. The clinical course in these patients was characterized by a rapidly progressive airflow obstruction, often unresponsive to therapy. Histological findings range from mild bronchiolar inflammation to progressive concentric fibrosis leading
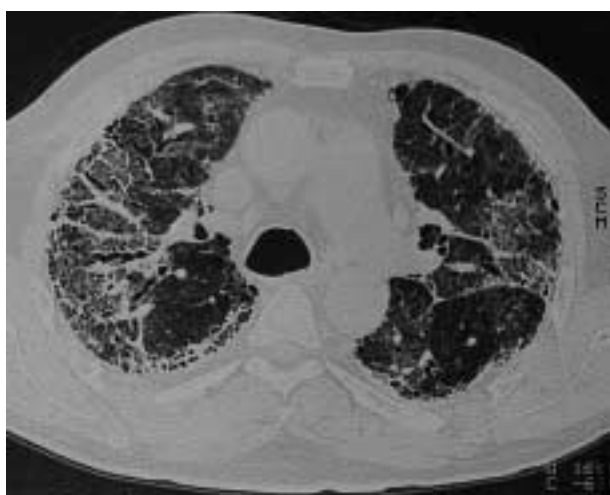

Fig. 2. – Rheumatoid arthritis. High-resolution computed tomography reveals extensive parenchymal involvement with irregular fibrotic changes containing honeycomb-like airspaces.

to complete occlusion [71]. Follicular bronchiolitis consisting of lymphoid hyperplasia and reactive germinal centers along small airways has also been described in RA [72].

Pathophysiology. Early histological studies demonstrated the presence of immune complexes in the alveolar walls, able to activate inflammatory cells, and in particular, alveolar macrophages. Important information was recently provided by several reports on the characteristics of BAL in asymptomatic patients, compared to patients with clinical ILD [73–77].

A neutrophil alveolitis is usually found in patients with clinical ILD, as defined by abnormal chest radiography and/or PFTs. The percentage of neutrophils in BAL fluid is correlated with the reduction of TL,CO [74]. Activation of polymophonucleates (PMNs) has been demonstrated by an increased release of myeloperoxidase, collagenase (in particular active type I collagenase that appeared to be of neutrophil origin) and elastase [75, 78]. GILLIGAN *et al.* [79] demonstrated that patients with overt ILD had a greater procollagen peptide concentration and collagenase activity in BAL fluid than those with early lung disease. The concentration of immune complexes is also markedly increased in BAL fluid [76]. Phagocytosis of local immune complexes could partly explain such activation of alveolar macrophages. BAL fluid histamine levels are markedly elevated in patients with ILD and are negatively correlated with TLC and VC [80]. Some patients with ILD also exhibited a marked increase in lymphocytes; BALBI *et al.* [81] demonstrated a preferential increase in Tec T-5,9+ T-cells, a subset of CD4+ lymphocytes responsible for many helper T-cell functions including the response to allogenic antigens. Such expansion might reflect the T-cell dependent increased stimulation of B-cells to produce immunoglobulins in the lungs of RA patients.

A subclinical lymphocytic alveolitis is found in approximately one-third of patients with normal chest radiograph and PFTs. Alveolar macrophages recovered from patients with subclinical alveolitis are activated and release increased amounts of superoxide anion, fibronectin and TNF-α. A similar alveolar macrophage activation is also found in patients with clinical ILD. IL-1β production was not different in these groups. The prognostic significance of subclinical alveolitis remains unknown, and BAL should probably not be included in the systematic assessment of RA patients without clinical, radiographic or PFT evidence of ILD. However, male sex, circulating antinuclear antibodies and peripheral blood CD4+ T-cells are good predictors of abnormal BAL findings and may be used to select high-risk patients [82].

A role for proteinase-antiproteinase imbalance in the development of interstitial lesions has been suggested by the demonstration that patients with non-M1M1 α1-antitrypsin phenotypes have an increased relative risk of ILD. A qualitative or quantitative defect in antiprotease activity could thus play a role in the maintenance of the local inflammatory process.

Management. In comparison with IPF, RA-associated ILD appears to have a better prognosis in most studies

[83] with a slower rate of deterioration in lung function [84]. However 5-yr survival rate was only 39% in a series of hospitalized patients [85]. A few cases of spontaneous remission have been described [86]. Conversely, fulminant cases have been reported despite inmunosuppressive therapy and plasmapheresis. Lack of response to treatment is usual in patients with intense gallium uptake in the lungs [87]. As in IPF, BAL lymphocytosis (>11%) indicates a favourable response to treatment, whereas alveolar neutrophilia predicts a poor outcome. However, persistence of alveolar neutrophilia during therapy is not synonymous with long-term clinical deterioration. In fact the best prognostic factor remains the findings at lung biopsy. Cellular inflammatory lesions (cellular interstitial pneumonia, DIP and lymphoid hyperplasia) appear reversible with treatment [88]. Despite this good prognostic value, open lung biopsy is performed rarely in patients with RA-related ILD; this approach is debatable and perhaps illogical.

The optimal therapeutic approach to RA-related ILD is not yet established. Corticosteroids are often used as a first-line treatment with regimens similar to those previously used in primary IPF. Initial therapy is usually prednisone 1 mg·kg^{-1}·day^{-1} for 6–8 weeks and subsequent dose tapering depends on clinical and PFT evaluation of early response. Results of corticosteroid treatment appear highly variable [61, 89] with an objective response rate of 44%, but when an initial response is obtained, it may be maintained in the long term. Methotrexate, azathioprine and cyclophosphamide have also been used in uncontrolled studies as primary treatment alone, or in combination with prednisone [90]. Alveolar neutrophilia and/or eosinophilia are predictive of a better response to cyclophosphamide than to corticosteroids. Lack of response to corticosteroids usually leads to alternative immunosuppressive therapy with a combination of corticosteroids and azathioprine, cyclophosphamide, or methotrexate [91]. Cyclosporin efficacy has been reported in an isolated case of aggressive fibrosis [92]. Single lung transplantation should be considered in end-stage ILD, although the possibility of recurrent disease cannot be excluded. However, it has to be kept in mind that the natural history of ILD in rheumatoid patients is more benign than in IPF, and that the disease may remain stable without therapy in a significant number of patients.

Bronchiolitis obliterans with organizing pneumonia

Cryptogenic organizing pneumonia (COP) was first decribed by DAVISON et al. [93]. Pathology was characterized by the presence of connective tissue in airspaces extending into alveolar ducts and occasionally into respiratory bronchioles. The same pathological entity was subsequently named bronchiolitis obliterans with organizing pneumonia (BOOP) by EPLER et al. [94] in a large series including five patients with collagen vascular diseases. BOOP was found in a variety of connective tissue diseases and predominantly in RA. RA was the underlying disease in five out of 29 cases of BOOP reported in Japan [95].

Pathological studies demonstrated BOOP lesions in six out of 40 lung biopsies from RA patients. The radiographical pattern in these patients was reticular-nodular and thus indistinguishable from IPF, while chest radiography in idiopathic BOOP usually shows patchy alveolar infiltrates. The course of the disease may be severe with rapidly progressive respiratory insufficiency [96]. Prognosis of CVD-associated BOOP appeared less favourable than idiopathic cases in one study, but several case reports described a good response to corticosteroids [97]. In addition, RA patients with BOOP had a better prognosis than those with ILD [66].

Necrobiotic nodules

Radiographically detectable lung nodules are found in about 0.2% of RA patients [98]. The frequency of pulmonary nodules is increased in males and patients with subcutaneous nodules or other extra-articular manifestations. In rare cases, nodules may precede the appearance of articular disease [99]. The radiographical size of these nodules ranges from a few millimeters to 7 cm; they are often peripheral with upper and midlung zone predominance (fig. 3).

Lung biopsy demonstrates the presence of nodules in 13 of 40 patients [66]. Nodules are most often located in subpleural regions or along interlobular septa, but endobronchial localizations have also been described. Histological findings are identical to those in subcutaneous nodules: the central zone consists of fibrinoid necrosis and is surrounded by palisaded histiocytes, giant cells, and occasionally, well-formed granulomas.

Invoked mechanisms of pathogenesis are vasculitis and immune complex deposition [100, 101]. Evolution of pulmonary nodules is unpredictable; they often remain stable or they may resolve spontaneously.
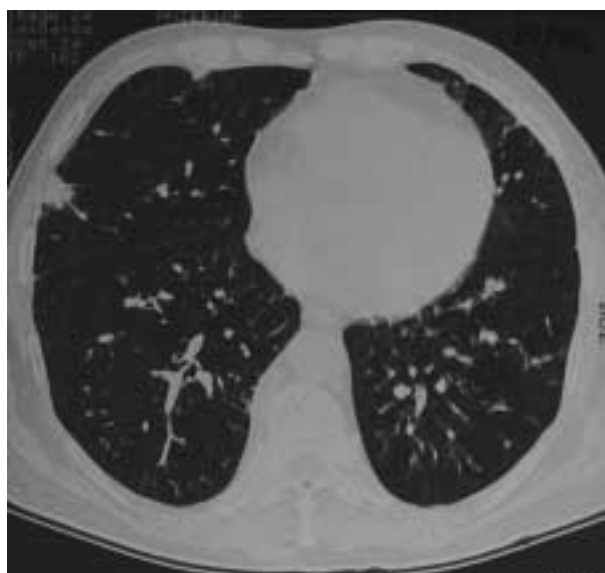

Fig. 3.–Rheumatoid arthritis. High-resolution computed tomography shows a rheumatoid nodule located subpleurally in the right lung.

Complications include cavitation, haemoptysis, pneumothorax and colonization by Aspergillus. Treatment of articular disease by second line drugs does not seem to alter the evolution of necrobiotic nodules, but corticosteroids are sometimes used in patients with compressive or rapidly growing lesions.

Rheumatoid pneumoconiosis

Rheumatoid pneumoconiosis, also known as Caplan's syndrome, is defined as the combination of multiple nodules and mining dust exposure in patients with RA [102]. Most patients have pre-existing mild pneumoconiosis (International Labour Office category 1). Histological findings are similar to those described in necrobiotic nodules, except for the presence of an additional peripheral pigmented dust ring surrounding the lesion [103]. Rheumatoid factor has been detected within the lung nodules. Relationships between pneumoconiosis and RA are well established. Circulating rheumatoid factors are found in ≤25% of patients with pneumoconiosis, and in 70% of those with Caplan's syndrome. Prevalence of RA is increased in patients with progressive massive fibrosis, and conversely, progressive massive fibrosis develops in 50% of miners with RA. However, the pathogenesis of rheumatoid pneumoco-niosis remains poorly understood.

Systemic lupus erythematosus

Acute lupus pneumonitis and alveolar haemorrhage

Clinical features. Although systemic lupus erythematosus (SLE) commonly involves the lung, occurrence of chro-nic pulmonary fibrosis is rare. More frequently lung manifestation in SLE results from acute injury to the alveolar-capillary unit, leading to acute lupus pneumonitis and/or alveolar haemorrhage [104, 105]. Acute lupus pneumonitis is an abrupt febrile pneumonic process without infectious aetiology. The alveolar haemorrhage varies from mild to massive, and BAL studies often reveal haemosiderin-laden macrophages. It presents with dyspnoea, tachycardia, cough, fever, pleuritic chest pain and sometimes haemoptysis. Chest radiographs typically show unilateral or bilateral patchy areas of consolidation, mostly predominant in the lung bases, which may be associated with pleural effusion or atelectasis.

Pathology and pathophysiology. Histological findings in acute lupus pneumonitis and massive pulmonary haemorrhage syndrome are quite similar, and include interstitial pneumonitis, hyaline membranes, alveolar necrosis, oedema, microvascular thrombosis and focal polymorphonuclear infiltration of arterioles and venules without evidence of vasculitis. Alveolar septal fibrosis may follow repeated episodes of pulmonary haemorrhage, suggesting that there is a continuum between acute and chronic ILD [106, 107]. Immuno-fluorescence studies have demonstrated granular deposits of immunoglobulin (Ig)G and C3 (the third

protein of the classical complement pathway) along the alveolar walls, the interstitium and endothelial cells [108], supporting the hypothesis that alveolar damage is mediated by immune complex deposition. Both deoxyribonucleic acid (DNA) and anti-DNA antibodies have been demonstrated in the immune complexes [108]. In addition, some data suggest that a chronic cell-mediated immune response may play a role in the pathogenesis of lung disease in SLE. Chronic interstitial pneumonia with a predominant lymphocytic infiltrate, as well as alveolar lympho-cytosis [109], have been described in some patients. In a small series of patients, the number of CD8 cells and CD56/CD16/CD3 (NK) cells obtained by BAL correlated inversely with the TL,CO [110], and high levels of nitric oxide (NO) have been found in the exhaled air of patients with SLE [111]. The cellular source of NO is unknown, but its presence is suggestive of an inflammatory process.

Management. Because infections predominate among the causes of death in SLE, the first step is to exclude infection as a cause of pulmonary involvement in SLE. MATTHAY *et al.* [104] recorded a 50% mortality rate from acute lupus pneumonitis. In the light of the pathological findings, corticosteroids, immuno-suppressive drugs and plasmapheresis have been used in the treatment of acute ILD in small and uncontrolled series. Corticosteroid therapy (1–2 mg·kg^{-1}·day^{-1}) associated with immunosuppressive drugs such as azathioprine (2–2.5 mg·kg^{-1}·day^{-1}) or cyclophospha-mide (2 mg·kg^{-1}·day^{-1}) have been widely reported to be beneficial. Little is known about the response in chronic fibrosis but it is thought to be poor [112].

Miscellaneous

There are several reports of BOOP occurring in patients with SLE and one autopsy series found organizing pneumonia in <20% of cases [113]. A small number of patients may develop a chronic form of ILD either *de novo* or after acute lupus pneumonitis.

Dermatopolymyositis

Clinical features of interstitial lung disease

Dermatopolymyositis (DPM) is often associated with clinical, radiological or functional evidence of pulmonary fibrosis. In two retrospective studies, ILD was found in 5% and 9% of DPM cases [114, 115]. Lung involvement in DPM may precede muscle or skin manifestations in 33% of cases. There is no correlation between the extent and severity of muscle and skin involvement and the development of ILD. The clinical presentation may be arbitrarily divided into three forms. 1) ILD may occasionally be rapidly progressive with acute fever, dyspnoea and lung infiltrates similar to a Hamman-Rich-syndrome. 2) Patients may have a slowly progressive dyspnoea upon exertion with chest radiographical abnor-malities. 3) Some patients may have no pulmonary

symptoms, but abnormal radiographs and/or PFTs. Chest radiographs most often reveal bilateral basal infiltrates, but may be normal in patients with biopsy proven ILD. HRCT shows pleural irregularities, ground glass attenuation and patchy consolidation (fig. 4) [116, 117]. PFTs demonstrate reduced FVC, TLC and TL,CO. Clinical exercise testing is of importance in DPM patients [118] to elucidate the cause of dyspnoea, which may not be limited to ILD, but might be due in part to pulmonary hypertension, cardiac dysfunction or muscle weakness.

There is no relationship between creatinine kinase or the extent of muscle disease and the development of ILD. Jo-1 antigen, precipitating antibody to an acidic nuclear protein antigen (histidyl-transfer RNA synthetase) has been reported to be a marker of associated-ILD in DPM, despite the fact that some patients are Jo-1 negative, but have ILD [119, 120]. Another study reported that antobodies to PL-7 (threonyl-transfer RNA synthetase) and to PL-12 (alanyl-transfer RNA synthetase) may be found in patients with DPM-related ILD.

Pathology and pathophysiology

Histopathological analysis of the lungs has been summarized recently [121]. Three major histological patterns are identified and include BOOP, UIP and DAD. In BOOP, inflammatory polyps protrude into the terminal bronchioles and young connective tissue extends from the terminal bronchioles into the alveolar structures. This pattern of lesion is associated with acute ILD, and is related to a better prognosis than chronic ILD. In chronic UIP, alveolar septal collagen deposition, sparse interstitial lympho-plasmocytic infiltrates and type II alveolar lining cell hyperplasia are seen. DAD is characterized by alveolar lining cell injury, alveolar wall oedema and intra-alveolar fibrin deposition, with formation of hyaline membranes and focal haemorrhages [122].
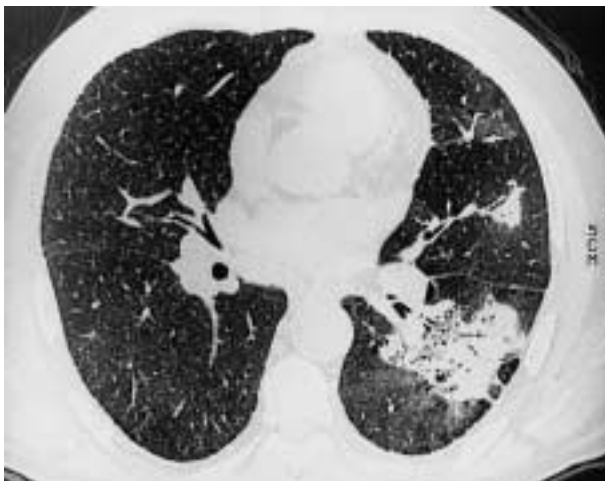

Fig. 4. – Dermatopolymyositis. High-resolution computed tomography at the level of the hila shows a bronchiolitis obliterans with organizing pneumonia pattern.

Management

Corticosteroids are thought to be effective in reversing the course of pulmonary disease, especially in those with acute onset of fever, dyspnoea and acute inflammatory ILD [123]. Patients with DPM-related UIP have a poorer outcome, with only a 33% survival rate at 5 yrs, compared to patients with DPM-related BOOP [122]. BAL appears in DPM as a reliable tool to assess alveolar inflammation. Accordingly, alveolitis as assessed by BAL is clearly associated with an active inflammatory process of the lower respiratory tract and progressive ILD [124]. There is little information regarding the effectiveness of immunosuppressive drugs in the treatment of ILD [125–128]. HATRON et al. [129] reported three cases of DPM-associated ILD demonstrating a good response to early treatment with corticosteroids (1 or 2 mg·kg^{-1}·day^{-1}) and cyclophosphamide (2 mg·kg^{-1}·day^{-1}). Management of therapy was based on clinical, radiological and physiological changes, and on the disappearance of alveolar inflammation as assessed by BAL. These results suggest that BAL may be useful in the clinical management of DPM-associated ILD [130]. Patients with abnormal neutrophil/ eosinophil alveolitis should be considered at high risk for developing ILD and should be treated early and followed carefully. Unfavourable prognostic signs include older age, a shorter disease history, dysphagia and the failure of the treatment to induce a remission [131].

Sjögren's syndrome

Obvious and clinically significant ILD is rare in the course of primary Sjögren's syndrome. A large series of 343 patients reported by STRIMLAN [132] clearly demonstrated that many patients do not manifest to a single type of pulmonary lesion. Sjögren's syndrome is at the crossroads of autoimmune diseases and lymphoproliferative disorders. Therefore, ILD may comprise lymphocytic pneumonitis, including pseudo-lymphomas and malignant lymphomas, and pulmonary fibrosis [133].

Pulmonary fibrosis is rather uncommon. The histopathological changes are poorly documented. In a series of 12 patients, lung lesions varied from a follicular bronchiolitis to a lymphoid interstitial pneumonitis to fibrosis with honeycombing [134]. In another study, involving 343 patients, histological findings were available in 13 subjects and demonstrated various lesions including two cases with pulmonary fibrosis, three with lymphocytic interstitial pneumonia, three with malignant lymphoma, one with pseudolymphoma, one with amyloidosis and four with bronchopneumonia [132]. Some cases of BOOP and two cases of diffuse panbronchiolitis have recently been reported [135].

It is likely that the incidence of lymphocytic pneumonitis is greater than generally believed. Using BAL, 29 patients with primary Sjögren's syndrome and 21 control subjects were studied by HATRON et al. [136]. Patients with Sjögren's syndrome showed an

increase in the percentage of lymphocytes and neutrophils. There were no differences in the percentage of eosinophils. On the basis of BAL findings, the patients with Sjögren's syndrome were classified as having no abnormalities or neutrophilic or lymphocytic patterns of alveolitis. Patients with alveolitis exhibited higher levels of gamma globulin, β_2-microglobulin and rheumatoid factor and antinuclear antibodies than patients with normal BAL. Better characterization of lung lymphocyte subtypes was provided by WALLAERT et al. [137]. An expansion of CD8+ lymphocytes was observed in patients with associated alveolar neutrophilia. In addition, patients with lymphocytic alveolitis with a reduced CD4+/CD8+ ratio exhibited more frequent cough, dyspnoea, radiological evidence of ILD and abnormal PFTs [138]. It has been demonstrated that natural killer activity is reduced in patients with primary Sjögren's syndrome, secondary to abnormal production of IL-2. MYASAKA et al. [139] found that pulmonary lymphocytes in Sjögren's syndrome have a decreased IL-2 production. Taken together, these findings support the theory of a lymphocyte-mediated inflammatory reaction in the lung, but the role of BAL in the clinical management of ILD associated with Sjögren's syndrome remains unclear.

Lymphocytic interstitial pneumonitis is thought to represent a benign lymphoproliferation in the lung, but also a premalignant state in some patients [140]. Histologically, it is characterized by an interstitial infiltrate of mature lymphocytes, plasma cells and other lymphoreticular elements. It coexists frequently with lesions of follicular bronchiolitis. Low-grade lymphoma is a potentially premalignant condition, the natural history of which is extremely variable [141].

There is little information to suggest that immunosuppressive drugs may improve pulmonary status in Sjögren's syndrome [142, 143]. Steroids and cytotoxic drugs may be given in patients with extra glandular involvement and are effective in approximately half of the patients. Chlorambucil has been reported to provide dramatic and complete response in some patients. In contrast, some patients with lymphocytic pneumonitis or pseudolymphomas may evolve into lymphoma, despite intensive chemotherapy.

Mixed connective tissue disease

Pulmonary involvement has been described in 20–85% of patients with mixed connective tissue disease (MCTD) [144]. The pathology and pathophysiology of ILD in MCTD is not well defined. Clinical features of ILD associated with MCTD are similar to those reported in scleroderma and consist of IPF with alveolar inflammatory processes and progressive development of honeycomb formation [145]; generally, the degree of fibrosis appeared more severe in patients exhibiting scleroderma features [145]. Pathological abnormalities of ILD in MCTD are similar to those seen in IPF, including alveolar septal infiltration by lymphocytes, plasma cells and type III collagen [146]. Abnormal PFTs and chest radiographs are frequent; impaired TL,CO has been reported in

67%, and restrictive lung volumes in 50% [147]. TL,CO appears to be the most sensitive single parameter in evaluating pulmonary dysfunction in MCTD. Corticosteroids and cytotoxic agents such as chlorambucil and cyclophosphamide are thought to be effective in acute inflammatory events. In a prospective study of 34 patients with MCTD, SULLIVAN et al. [144] demonstrated a favourable response in two-thirds of them. However, in another study, some patients, especially those with predominantly scleroderma-like disease, did not respond to steroids or immunosuppressive drugs [145]. Surprisingly some patients exhibited resolution of pulmonary opacities with nonsteroidal drugs.

Conclusions

Different types of interstitial lung disease (e.g. usual interstitial pneumonia, desquamative interstitial pneumonia, nonspecific interstitial pneumonia, lymphocytic interstitial pneumonia, organizing pneumonia, diffuse alveolar damage) may be present in several forms of collagen vascular disease, including scleroderma, rheumatoid arthritis, systemic lupus erythematosus, dermatopolymyositis, Sjögren's syndrome and mixed connective tissue disease. The clinical presentation, the prognosis and response to therapy vary depending on the histological pattern of interstitial lung disease, as well as on the underlying collagen vascular disease.

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