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REVIEW

Pivotal clinical dilemmas in collagen vascular diseases associated with interstitial lung involvement

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ABSTRACT: The connective tissue disorders (CTDs), also called collagen vascular diseases (CVDs), represent a heterogeneous group of immunologically mediated inflammatory disorders with a large variety of affected organs. Individuals with a CTD (rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome, polymyositis/dermatomyositis and mixed connective tissue disease) are susceptible to respiratory involvement. When the lungs are affected, an increasing mortality and morbidity in CVDs occurs. Interstitial lung disease (ILD) is established as a clinical corollary across the spectrum of CTDs, with an overall incidence estimated at 15%.

Therefore, pivotal clinical dilemmas remain in the evaluation and management of ILD involvement in CVDs. Critical questions are the presence of fibrosis and whether the disease is clinically significant. Moreover, the clinician has to decide if treatment is warranted and which is the best therapeutic approach. The use of additional tests, such as pulmonary function tests, high-resolution computed tomography scan, bronchoalveolar lavage fluid and surgical lung biopsy, deserves better discussion. The present review focuses on establishing the diagnosis of ILD in CTD, and on evaluating disease activity and prognosis. This will provide the basis for therapeutic decisions that will be discussed, including an overview of recent advances.

KEYWORDS: Bronchoalveolar lavage fluid, collagen vascular diseases, connective tissue disorders, interstitial lung disease, pulmonary fibrosis, treatment

The connective tissue disorders (CTDs), also called collagen vascular diseases (CVDs), represent a heterogeneous group of immunologically mediated inflammatory disorders with a large variety of affected organs. Individuals with a CTD (rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), Sjögren's syndrome (SS), polymyositis (PM)/dermatomyositis (DM) and mixed connective tissue disease (MCTD)) are susceptible to respiratory involvement.

All components of the respiratory system may be affected, *i.e.* airways, vessels, parenchyma, pleura and respiratory muscles. The frequency, clinical presentation, prognosis and response to therapy vary, depending on the pattern of involvement along with the underlying CTD. Interstitial lung disease (ILD) is an established clinical corollary across the spectrum of CTDs, with an overall incidence estimated at 15% (table 1). Rates of ILD differ between these CTDs. Using high-resolution computed tomography (HRCT) to detect ILD in CTD patient cohorts (cohort sizes ranging 21–156), prevalence varies from 19% in RA to 67% and 85% in MCTD and diffuse SSc, respectively [1–3]. Intermediate prevalence, in the range 23–38%, is found in SLE and DM/PM. Interstitial lung involvement is usually referred to as interstitial pneumonia (IP). IPs can be further subdivided into several histopathological/radiological entities: nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organising pneumonia (OP), respiratory bronchiolitis-associated ILD, desquamative IP, diffuse alveolar damage (DAD) and lymphocytic interstitial pneumonia (LIP). Classification of NSIP has been further subdivided in two groups, namely cellular and fibrotic NSIP [2]. As all seven pathological types are also seen in CVD-IP, the same classification is applied.

Early detection of pulmonary involvement is very important for the initiation of targeted therapy, because the damage to the lung parenchyma may

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TABLE 1 Interstitial lung involvement in connective tissue diseases

Rheumatoid arthritis	Usual interstitial pneumonia
	Nonspecific interstitial pneumonia
	Organising pneumonia
	Rheumatoid nodules
Systemic sclerosis	Nonspecific interstitial pneumonia
	Usual interstitial pneumonia
Sjögren's syndrome	Nonspecific interstitial pneumonia
	Lymphocytic interstitial pneumonia
	Usual interstitial pneumonia
	Desquamative interstitial pneumonia
Polymyositis/dermatomyositis	Lymphocytic interstitial pneumonia
	Organising pneumonia
	Diffuse alveolar damage
Systemic lupus erythematosous	Acute interstitial pneumonitis
	Lymhocytic interstitial pneumonia
	Nonspecific interstitial pneumonia
	Usual interstitial pneumonia
	Desquamative interstitial pneumonia

already be irreversible at the time of the onset of respiratory symptoms. It is now recommended that all patients with CVD are checked for IP [1, 3]. Routine checking includes clinical evaluation, lung function and clinical exercise tests, imaging modalities, bronchoalveolar lavage (BAL), lung biopsy and use of some serum biomarkers.

Conversely, ILD may be the first or sole recognised manifestation of a CTD. As the clinical features of the CTDs may be subtle, it is often difficult for clinicians to identify an underlying CTD in individuals who present with ILD. It can be especially challenging to accurately characterise patients with subtle manifestations of CVDs. However, in some patients, lung involvement precedes other systemic symptoms, making the distinction between idiopatic NSIP and lung involvement of CTD impossible at the time of diagnosis. It is plausible that a significant proportion of idiopathic NSIP is undifferentiated CTD, a clinical entity with symptoms and/or signs of a CTD, but not fulfilling the classification of any specific diagnostic entity [4].

RHEUMATOID ARTHRITIS

RA is a systemic destructive, inflammatory disease affecting ~1–2% of the general population [1, 3]; the most common CVD [3]. Nearly 50% of the patients present extra-articular manifestations involving skin, eye, heart and lungs [5, 6]. Clinically, these manifestations are dominated by pulmonary, cardiac and vascular changes. Although cardiovascular disease is responsible for the majority of RA-related deaths, pulmonary complications are common and cause 10–20% of overall mortality [6]. The majority of lung disease occurs in the first 5 yrs after initial diagnosis, and may be the presenting manifestation in 10–20% of patients. The most common pulmonary manifestations are pleural abnormalities and ILD [2]. The prevalence of ILD in RA varies depending on the criteria used to establish the diagnosis.

Histopathology

Unlike in most other CTDs, in RA the UIP pattern is more commonly seen on surgical lung biopsy than NSIP [7, 8]. RA patients who develop pulmonary fibrosis are often younger than those with idiopathic UIP. Cigarette smoking has been reported to be an independent predictor of lung disease in RA [9]. In the study by LEE *et al.* [7], 42 patients with RA underwent lung biopsy and were diagnosed as having IP. In 70% of these patients HRCT findings, such as lower lobe-dominant bilateral subpleural reticular opacities with honeycombing and absence of ground glass opacities, supported the evidence of an UIP pattern. In the study by YOSHINOUCHI *et al.* [8], most patients with UIP pattern on biopsy had honeycombing and reticulonodular opacities on HRCT, whereas patients with NSIP had no honeycombing on HRCT. Only in the study by TANAKA *et al.* [10] NSIP was observed to be the predominant pattern on lung biopsy, but only four out of 26 patients with UIP pattern on HRCT underwent lung biopsy. LIP and OP have also been described [11, 12]. In addition, acute interstitial pneumonia (AIP) is quite uncommon in RA [13, 14].

The above pathological patterns described in RA-ILD have prognostic significance. Recently, PARK *et al.* [15], in a large series of 362 patients (269 patients with IP and 93 with CVD), have observed that prognosis in patients with CVD-UIP is better than in patients with idiopathic pulmonary fibrosis (IPF)-UIP. As a subgroup, the RA patients with IP also had a better prognosis than those with IPF, despite the same histopathological pattern of UIP [13].

More than any other rheumatic disease, patients with RA-associated lung disease tend to manifest concurrent acute, subacute and chronic histopathology, all in the same surgical biopsy. Thus, a combination of acute, subacute and chronic inflammatory reactions, including involvement of the pleura, should always raise consideration of RA disease. Vasculitis and pulmonary haemorrhage have been described as acute pulmonary manifestations of RA. Rheumatoid nodules may be difficult to distinguish from granulomatous infection and Wegener's granulomatosis. Knowledge of the clinical and radiological findings is often helpful in resolving this dilemma.

Clinical and laboratory features

Symptoms of RA usually precede lung involvement, but they can occur simultaneously, or RA can follow the diagnosis of IP [8, 16, 17]. The most frequent respiratory symptoms are progressive dyspnoea and dry cough even if, in many cases, dyspnoea on exercise may be masked by inactivity due to polyarthritis. Most patients have fine bibasilar crackles, but clubbing is less common than in patients with IPF [18].

Pulmonary function tests (PFTs) are invaluable in identifying CTD patients likely to have underlying ILD or pulmonary vascular disease. The most used parameters are total lung capacity (TLC), vital capacity (VC), forced expiratory volume in one second and diffusing capacity of the lung for carbon monoxide ($D_{L,CO}$). Among routine PFTs, $D_{L,CO}$ is the most sensitive variable; a restrictive defect is typical but mixed patterns may also be seen [19, 20]. Reductions in volumes (especially the forced vital capacity (FVC) or TLC) are less sensitive.

A reduced $D_{L,CO}$ may predict the progression of lung fibrosis, and DAWSON *et al.* [21] showed that a $D_{L,CO}$ <54% of the predicted value is a highly specific predictor of disease progression. In case of normal lung volume, a reduced $D_{L,CO}$ may indicate pulmonary vascular disease.

Peak and functional exercise capacity are reduced in patients with CVD-IP, and this can be observed during cardiopulmonary exercise testing (CPET). Reduction in ventilatory capacity and gas exchange are the cause of reduction in exercise capacity. CPET is very important because it can help the diagnosis in early stage disease in patients with normal PFTs, normal chest radiography or normal HRCT by detecting an exercise-induced hypoxaemia and an increase of alveolar–arterial oxygen gradient [22, 23]. Arterial desaturation can be observed using a 6-min walk test and pulse oximetry, even if hypoxaemia and desaturation might be hidden by hyperventilation [24, 25]. However, the aforementioned methodology gives a crude indication of a patient's exercise capacity, although myositis, wasting, anaemia, arthralgias and/or cardiac involvement may pose limiting factors.

Radiological features

The value of chest radiography is limited in the diagnosis of CVD-IPs. The HRCT findings in RA can be categorised as parenchymal, airways and pleural disease. HRCT is more specific and sensitive for the identification of IP and is abnormal in >80% of patients with RA and suspected IP [26].

The pattern of radiographic abnormality seen on HRCT in RA has proved to be an excellent predictor of the underlying pathological pattern. Four radiographic patterns have been described: UIP, NSIP, OP and bronchiolitis. Three of the radiographic patterns, UIP, NSIP and OP, conform to those seen in idiopathic interstitial pneumonias (IIPs), and strongly correlate with the underlying pathology [14]. In detail, in patients without respiratory symptoms the prevalence of ground glass opacities is 3% and the prevalence of honeycombing is 0%, in contrast to 26% and 23%, respectively, in patients with respiratory symptoms [27]. However, there is one study which claims that the majority of the changes observed in HRCT are nonspecific and in only one patient has a pattern suggestive of IP been seen [28]. In patients with early onset RA the prevalence of IP is 33%; a pattern of ground glass opacities is the most frequent [27, 29]. However, most studies have shown that a reticular pattern with honeycombing is a more frequent finding on HRCT than ground glass opacities, regardless of histological subtype [14, 19, 30–32]. Similar to the pathological patterns, these radiographic patterns also appear to predict progression and outcome in RA-ILD [19, 33]. In the study by TANAKA *et al.* [10], four patterns have been found to be more frequent; UIP, NSIP, OP and bronchiolitis. The lung biopsy in 17 patients revealed a histological pattern that reflects the findings of HRCT.

Bronchoalveolar lavage

BAL is not routinely used as a diagnostic modality in RA-associated ILD. The main value of BAL is to exclude complicating infections and malignancy, and to identify unusually high counts of one or more cell types indicating the possibility of coexisting disease (*e.g.* a striking eosinophilia could suggest a drug reaction in the appropriate clinical context). BAL can be abnormal in 52% of the patients with early onset RA revealing the presence of alveolitis [27]. A neutrophil alveolitis can be found in patients with clinically evident IP [31, 34, 35] and a lymphocitic alveolitis can be found in 33% of patients with normal chest radiography and PFTs [34].

Lung biopsy

Lung biopsy has an important role in the prognosis of IIPs but the fact that UIP seems to be rare in CVDs, with the possible exception of RA [36], and that the prognosis of CVD-UIP seems to be better than in IPF-UIP, has put in doubt that open lung biopsy is justified in patients with CVD-IIP, because its prognostic significance seems to be low.

Treatment

As far as the treatment of RA-IP is concerned, unfortunately there have not, as yet, been any randomised controlled trials. Therefore, therapy is essentially empirical. Corticosteroids are the first line therapy (prednisone 0.5–1 $mg \cdot kg^{-1}$) and the best response has been observed in patients with RA-OP [37]. Immunosuppresive drugs such as azathioprine, cyclosporine, methotrexate (MTX) and cyclophosphamide are also used, either in association with corticosteroids for maintenance therapy or for corticosteroid-resistant forms.

The use of MTX in RA has been associated with MTX pneumonitis (MTX-P), which is observed in 0.5–12% of patients with RA [38]. There are three sets of criteria for the diagnosis of MTX-P [39–41]. The accepted changes of MTX-P on HRCT of the chest are patchy ground glass shadowing in any part of the lung that can be associated with micronodule formation and lymphadenopathy [42, 43]. As HRCT is noninvasive and widely available, this investigation should be performed as soon as is feasibly possible in order to identify the correct diagnosis. If HRCT is not diagnostic then BAL and/or lung biopsy should be considered. BAL studies suggest that a lymphocytic BAL differential, particularly with an increased proportion of CD4+ cells, supports the diagnosis of MTX-P [44]. However, BAL, HRCT and lung biopsy data need further elaboration before the diagnosis of MTX-P can be made because the whole clinical picture can be blurred by the presence of CTD-associated ILD. Moreover, an important issue is that infection, as a reason for deterioration, needs to be excluded. MTX-P is not related to the cumulative or weekly dose of MTX and can even occur up to 4 months after discontinuation of the drug [45, 46]. In patients with RA resistant to MTX therapy, tumour necrosis factor-α blocking agents can be used (*i.e.* etanercept, infliximab and adalimumab) [47–49]. Infliximab has been found to stabilise the progression of pulmonary fibrosis associated with RA [50]. These drugs can also be used in RA patients with early disease [51]. They are well tolerated and the side-effects include local reactions at the injection site, upper respiratory tract infections and an increased susceptibility to tuberculosis. A fatal exacerbation of RA-associated fibrosing alveolitis in patients treated with infliximab has also been described [52]. Cyclosporine has been used to treat both acute pneumonitis and progressive pulmonary fibrosis with success in individual patients [53–56]. RA-IP patients can attain some benefit with long-term oxygen therapy and respiratory rehabilitation [1, 3, 6]. Lung transplantation is the final modality in late-phase RA-IP without other organ involvement.

SYSTEMIC SCLEROSIS (SCLERODERMA)

SSc is a collagen tissue disorder in which pulmonary involvement is very frequent and is associated with poor prognosis [57–59]. The most common pulmonary complications are fibrosing alveolitis of systemic sclerosis (FASSc), and pulmonary vascular disease, which is the leading cause of death in SSc [60], surpassing renal involvement. In SSc, 25% of all patients will develop clinically significant ILD and severe restrictive lung disease has been reported in 13% [57–59]. Therefore, the identification and staging of pulmonary involvement is very important for the management of the disease. For many years, IPF and FASSc were considered to be histologically similar conditions, despite the better prognosis in FASSc [61]. Recent studies in SSc demonstrated that NSIP is the most common histological pattern, followed by UIP in SSc [62–64].

Clinical and laboratory features

There are two forms of SSc. One is limited SSc (70%), with subcutaneous calcinosis, Raynaud's phenomenon, esophageal dismobility, sclerodactily and telangiectasias. The presence of positive circulating anticentromere antibodies is 70%. Pulmonary hypertension is common in limited SSc. The second is diffuse SSc, in which cutaneous involvement occurs simultaneously with the Raynaud's phenomenon, antitopoisomerase antibodies are present in 30% of the patients and anticentromere antibodies are usually absent (present in 3% of the patients). ILD occurs in limited or diffuse SSc and lung involvement rarely precedes scleroderma, although there is a syndrome called SSc sine scleroderma described in patients exposed to inhaled mineral particles [65]. In addition, it has been reported that at the presentation of an IIP, the presence of a nucleolar-staining antinuclear antibody, telangiectasia, Raynaud's phenomenon with abnormal capillaroscopy findings, gastro-oesophageal reflux or pericardial disease, suggests underlying SSc [66]. These findings should assist clinicians in the evaluation and treatment of patients with otherwise undefined ILD. Furthermore, coexistence of one or more autoimmune diseases and sarcoidosis has been described in the literature [67].

Respiratory symptoms include dry cough and dyspnoea, even if dyspnoea on exercise may be masked by general debility. As mentioned for RA, PFTs are very important for the evaluation of pulmonary involvement in SSc. $D_{L,CO}$ levels correlated better than other lung function indices with the total morphological extent of disease on HRCT [68]. In limited SSc, an isolated reduction of $D_{L,CO}$ can be associated with pulmonary vascular disease and can be a predictor for the development of pulmonary hypertension [69]. It is believed that a reduction of $D_{L,CO}$ level below 50% of the predicted value is an important indication for the initiation of therapeutic intervention. Cardiopulmonary exercise testing and 6-min walk distance are also important for the evaluation of the functional status of SSc patients [24], they can identify factors limiting exercise [70, 71], evaluate the effect of pharmacological or nonpharmacological interventions [72] and predict survival [73]. However, they do not lack cardinal limitations.

Radiological features

In CVD-IP, chest radiography has a limited value. In contrast, HRCT has a greater sensitivity and improves the diagnosis. Although the imaging features of SSc-associated ILD have been extensively studied [74], more recent work with HRCT, together with the reclassification of the IPs, has led to a greater understanding of the condition. Currently, the consensus is that NSIP is the most common subtype, knowledge in part based on information obtained from HRCT studies, given that lung biopsies are performed only in a minority of cases. In a study of 225 patients, DESAI *et al.* [75] showed that the HRCT findings in SSc most closely resembled those of NSIP, typified by a predominant pattern of ground glass opacification and fine reticular opacities. HRCT has also been used to study longitudinally the lung disease in scleroderma. In a recent study, LAUNAY *et al.* [76] followed patients with predominantly ILD over a 5-yr period. They reported that approximately half of patients with ground glass abnormalities at initial computed tomography (CT) progressed to coarser fibrosis and honeycombing, whereas only 15% of subjects with a normal initial CT showed evidence of progression at 5 yrs.

Bronchoalveolar lavage

BAL is a valuable diagnostic tool for ruling out infection or confirming the presence of alveolitis. Alveolitis can be operationally defined as an increase in neutrophils >3% or eosinophils >2% of total cells on the BAL cell differential count. The prognostic value of BAL neutrophilia is questionable. On one hand, there are studies that have observed that BAL neutrophilia is associated with more progressive disease, especially in untreated patients, and therapy with oral cyclophosphamide has found to be associated with a better outcome [77–79]. Based on these data, BAL should be performed routinely in FASSc and have an important role on therapeutic decisions [80]. In addition, previous studies have shown that BAL neutrophilia is generally associated with extensive fibrotic disease, whereas a BAL eosinophilia is often seen in less advanced disease, particularly when CT appearances suggest lung inflammation [81, 82].

However, in a very recent study by GOH *et al.* [83], in which BAL cellular profiles have been studied in patients with SSc-IP, it has been shown that BAL findings do not have a prognostic value in disease progression, once disease severity is quantified by PFTs and HRCT. Early mortality (occurring within 2 yrs of presentation) is associated with BAL neutrophilia independent of disease severity, whereas late mortality (occurring 2–10 yrs after presentation) is not associated with BAL neutrophilia. As far as the other constituents of BAL are concerned, both BAL eosinophilia and lymphocytosis are not associated with mortality, rapidity of functional deterioration, or progression-free survival. These findings are unaltered when treatment status is taken into account [83]. In order to evaluate whether lavage cellularity identifies distinct subsets of disease and/or predicts cyclophosphamide responsiveness, lavage was performed in 201 patients as part of a randomised placebo-controlled trial of cyclophosphamide *versus* placebo (Scleroderma Lung Study) [84]. Abnormal cellularity was present in 101 of these cases and defined a population with a higher percentage of males, more severe lung function, more extensive ground glass opacity and more extensive fibrosis in the right middle lobe. Despite the aforementioned relationships, the presence or absence of an abnormal cell differential was not found as an independent predictor of disease progression or response to cyclophosphamide at 1 yr [85].

The conclusion that BAL has little to offer in routine prognostic evaluation in SSc-ILD is based upon the similarity of findings in these separate cohorts, with varying methodologies and analytic strategies, complementary strengths and differing limitations. Nevertheless, because of variability in reporting of cell counts and difficulties in interpretation, treatment decisions should not be based on BAL findings alone. A limited role for BAL cannot be wholly discounted if there is uncertainty regarding treatment decisions following routine staging, but this applies to highly selected patient subgroups and has not been captured in recent analyses.

Lung biopsy

The study by BOUROS *et al.* [62] has shown that in 80 patients with lung biopsy-proven SSc-ILD, 5-yr survival differs little between UIP/end-stage lung disease (82%) and NSIP (91%), or between the subtypes of NSIP (cellular and fibrotic). Survival was linked to the level of lung function impairment, BAL eosinophil levels, and changes in $D_{L,CO}$ (but not FVC) during the first 3 yrs of follow-up. In a smaller series (19 patients), KIM *et al.* [64] have observed that the prognosis of NSIP is better than the prognosis of UIP. In conclusion, lung biopsy is less warranted as far as prognostic evaluation of SSc is concerned, except in cases with unusual HRCT appearances.

Serum biomarkers

The most promising markers implicated in the diagnosis, prognosis, choice and response to treatment in SSc are serum surfactant proteins (SPs) A and D, and mucine-like high molecular weight glycoprotein Krebs KL-6, which are produced by alveolar type-II epithelial cells. In one study, it has been observed that the concentration of SP-A and SP-D were significantly higher in patients with SSc-IP than in SSc patients without IP [86]. KL-6 has been also found to be higher in patients with SSc-IP than in patients without IP and healthy controls. Serum levels of these biomarkers have shown to inversely correlate with VC and $D_{L,CO}$ levels [87]. However, its sensitivity and specificity regarding disease activity is unclear, as increased serum and BAL levels of KL-6 are found in a variety of ILDs.

Autoantibodies such as anticentromerase and antitopoisomerase-I are thought to be more useful in predicting the development of IP than the nature of the skin disease [88, 89]. In fact, in patients with limited SSc and anticentromere antibody positivity, severe pulmonary fibrosis is rare, whereas patients with diffuse SSc and antitopoisomerase positivity need to be strictly monitored in order to initiate an early treatment.

Treatment

Until recently no proven effective therapy to prevent disease progression or reverse fibrosis existed. Corticosteroids represent one of the first-line drugs used in the therapy of SSc-IP, despite the fact that evidence of their efficacy is lacking. These drugs are also associated with scleroderma renal crisis (SRC), which was first shown in the study by STEEN and MEDSGER [90]. A dose of 15 mg·day^{-1} of prednisone over a period of 6 months was associated with SRC. In the study by DEMARCO *et al.* [91] it has been observed that prednisone was associated with SRC only when high skin scores and large joint contractures were present, but surprisingly the mean dose was only 7.4 mg·day^{-1}. The efficacy of oral cyclophosphamide has been studied by WHITE *et al.* [79] who observed that oral administration of the drug in patients with BAL neutrophilia was associated with stabilisation or improvement in FVC and $D_{L,CO}$ and a better survival than in untreated patients, whereas in treated patients the outcome was similar to that in untreated patients without BAL neutrophilia.

Two prospective placebo-controlled multicentre clinical trials have been recently completed in SSc patients with alveolitis. The North American Scleroderma Lung study evaluated the efficacy of 12 month's oral cyclophosphamide 2 mg·kg^{-1} *versus* placebo in 162 patients [84]. The main outcome measure was change in FVC % pred. Secondary outcome measures included changes in TLC and $D_{L,CO}$ % pred, and several measures of dyspnoea, quality of life and functional indices. It was found, at 12 months, that patients treated with cyclophosphamide had significantly less change in FVC compared with placebo-treated patients. Oral cyclophosphamide also had a beneficial effect by improving dyspnoea, functional ability, health-related quality of life and skin thickness [84]. The group of oral cyclophosphamide had more adverse effects due to the drug such as leukopenia and neutropenia than the placebo group but the risk/benefit ratio seems to be favourable [84]. A second year of follow-up was performed in order to determine if these effects persisted after stopping treatment [92]. Using a longitudinal joint model, the authors analysed FVC, TLC, transitional dyspnoea index, Rodnan skin scores and the Health Assessment Questionnaire Disability Index during the second year after adjusting for baseline values, baseline fibrosis score and nonignorable missing data. It was found that, except for a sustained impact on dyspnoea, all other effects waned and were no longer apparent at 24 months.

Intravenous administration of cyclophosphamide is preferred to oral administration because of the lower risk of toxicity and, particularly, of bladder cancer. Intravenous administration of cyclophosphamide seems to have less adverse effects [93]. There are three studies in which efficacy of *i.v.* cyclophosphamide administered for 6 months (once monthly), in combination with corticosteroids in patients with SSc-IP has been studied [94–96]. The Fibrosing Alveolitis in Scleroderma Trial, conducted in the UK, investigated the effects of prednisone (20 mg *q.o.d.*) with six infusions (monthly) of *i.v.* cyclophosphamide 600 mg·m^{-2} followed by oral azathioprine, *versus* matched placebo [97]. At 12 months there was a statistically significant difference in active treatment *versus* placebo in FVC. This treatment difference was 4.76% favouring cyclophosphamide compared with placebo ($p=0.04$) [97].

Most importantly, outcomes in both studies [84, 97] clearly show that in SSc-ILD, the treatment effect largely represents the prevention of progression of fibrotic disease.

Endothelin is overexpressed in two forms of ILD: IPF and pulmonary fibrosis due to scleroderma. Endothelin blockade with bosentan may provide a new treatment opportunity. Trials with bosentan in IPF (the BUILD (Bosentan Use in Interstitial Lung Disease)-1 trial) and pulmonary fibrosis secondary to scleroderma (BUILD-2) were initiated in 2003. In November 2005, the results of the studies showed that

bosentan had no effect on the primary end-point of exercise improvement as measured by the 6-min walk test. The fact that in BUILD-2 no effect on either primary or secondary outcomes was shown could be related to the slow progression of the disease (pulmonary fibrosis related to SSc) observed in the study population, which was in contrast to the more severe and more rapidly progressive disease observed in BUILD-1. In conclusion, bosentan should not be used in SSc-ILD.

SJÖGREN'S SYNDROME

SS is an inflammatory CTD that is characterised by lymphocytic infiltration of the exocrine glands resulting in the sicca syndrome [98]. SS can occur alone as primary SS (pSS) or in association with other CVDs, such as RA, SLE and progressive SSc, known as secondary SS [99]. pSS may also have extraglandular manifestations affecting pulmonary, renal and small vasculature [100]. The frequency of pulmonary involvement varies from 9% to 75% depending on the detection method employed, and consists of various forms of small airway disease and ILDs [101–104]. Various histological patterns of ILDs have been associated with pSS, such as NSIP, UIP, OP, LIP, primary pulmonary lymphoma and diffuse interstitial amyloidosis. In earlier studies, it has been observed that LIP and primary pulmonary lymphoma were the dominant patterns in patients with pSS-IP [101–104]. Pulmonary lymphomas, which may present as solitary or multiple opacities, nodules or masses, and diffuse interstitial lesions with cysts in some cases may be indistinguishable from other benign lesions, such as LIP [105]. In recent studies it has been observed that NSIP is the most frequent pattern [106, 107]. This difference may be explained by the recent revision that took place in the recent classification criteria for IIPs [1] and, because of this, some cases previously classified as LIP may be now classified as NSIP.

Clinical and laboratory features

According to American–European classification criteria, the diagnosis of pSS is based on the following items: ocular symptoms of inadequate tear production, ocular signs of corneal damage due to inadequate tearing, oral symptoms of decreased saliva production, salivary gland histopathology demonstrating foci of lymphocytes, test results indicating impaired salivary gland function, and the presence of autoantibodies (anti-SS-A/Ro or anti-SS-B/La, or both). Definite diagnosis requires the presence of four of the six items with histopathological findings or autoantibodies being one of the four items [108]. Pulmonary manifestation most commonly includes exertional dyspnoea and dry cough with inspiratory crackles being the most frequent finding on physical examination. PFTs usually indicate a restrictive pattern with a decrease of $D_{L,CO}$, TLC [109] and VC [104].

Radiological features

Data regarding the extent and incidence of respiratory involvement in SS vary widely depending on the methodologies used to investigate the disease. In patients with pSS, it has been found that bilateral lung infiltrates is the most common pattern seen on chest radiography [109]. It also has been found that in patients with both pSS and secondary SS, 22% had chest radiography abnormalities, with linear and reticular opacities being the most frequent finding [110].

HRCT findings in SS include both interstitial and airway abnormalities. The most commonly observed signs are ground glass opacities, nodules and thin-walled cysts [74]. This combination of signs is in accordance with LIP. In the study by MATSUYAMA *et al.* [110] in patients with both pSS and secondary SS, it has been observed that centrilobular abnormalities and lymphoproliferative disorders pattern were characteristic in patients with pSS.

Honeycombing and pulmonary fibrosis are reported to be relatively uncommon features of SS [75]. In the study by PARAMBIL *et al.* [109], in a retrospective analysis of 18 patients with pSS, HRCT features appeared to correlate relatively well with the underlying histopathological pattern of ILD. PARAMBIL *et al.* [109] also found that NSIP and OP were the most common pathologies, with UIP and LIP being less frequent. This would be consistent with the HRCT observation (in other nonbiopsy studies) in which ground glass opacities and consolidation were the predominant patterns [74]. In addition, HRCT–pathological correlation resulted in a 94% positive predictive value of CT-NSIP pattern for pathological diagnosis of NSIP, and the 5-yr survival rate was found to be 83% in patients with NSIP [105]. In contrast, the diagnostic value of HRCT was low (15%) with a HRCT pattern other than NSIP, data that may influence the decision to perform a biopsy [105].

Bronchoalveolar lavage

BAL has demonstrated the high prevalence of subclinical lymphocytic and neutrophilic alveolitis, affecting 50% of patients with SS [111]. Alveolitis is more frequent in patients with extrapulmonary involvement. Neutrophilic alveolitis and an increase of CD8+ T-lymphocytes are associated with alteration of lung function [112, 113].

Lung biopsy

As previously mentioned, lung biopsy no longer has a place as a diagnostic procedure for CVD-IPs and adds little to the prognosis of the disease. In patients with SS-IP, lung biopsy is rarely required, with the exception of cases with HRCT patterns other than NSIP, because the diagnostic value of HRCT is low in these cases. So, these patients may have to undergo lung biopsy in order to diagnose or exclude malignant lymphoma [104].

Serum biomarkers

The presence of autoantibodies, and particularly anti-SS-A/Ro and anti-SS-B/La, is crucial for the diagnosis of SS. Other useful laboratory markers include polyclonal hypergammaglobulinaemia, elevated erythrocyte sedimentation rate, elevated titre of rheumatoid factor and the presence of antinuclear antibodies.

Treatment

Currently there is no consensus for the treatment of SS. Corticosteroids are commonly used as first-line therapy. Pulmonary symptoms seem to improve within several weeks but improvement in PFTs and radiological findings occur over a course of few to several months [109]. Among the histopathological patters of SS, OP seems to respond better to corticosteroid therapy. Immunosuppressive agents such as azathioprine and cyclophosphamide can also be used but their role in the therapy of SS-IP is not yet clear.

POLYMYOSITIS/DERMATOMYOSITIS

PM and DM are systemic inflammatory diseases affecting skeletal muscles and other organs, especially the lungs. Pulmonary involvement in PM/DM may precede muscle and skin manifestations and includes respiratory muscle weakness, aspiration pneumonia, ILD, ventilatory insufficiency, infections and drug-induced pneumonia [114–117]. ILD, which develops in 23.1–65.0% of PM/DM patients [116, 118–120], is a major cause of death in this disease [116, 119, 121–123]. ILD leads to life-threatening complications, such as ventilatory failure, secondary pulmonary arterial hypertension and cor pulmonale [116, 117, 121, 122, 124–127], so the early detection of ILD is a high priority in PM/DM patients. However, in PM/DM patients a careful search for underlying malignancies is strongly advocated. Poor prognostic factors of ILD in PM/DM have been reported to include a Hamman-Rich-like pattern, low creatine kinase levels, low $D_{L,CO}$, neutrophilic BAL and lung histology of DAD or UIP [119, 123, 128, 129]. The 3-yr mortality rate of the chronic-type patients (21.2%) was not found to be significantly different from that of the patients without ILD (10.2%) [130]. In addition, the acute, severe form of ILD is not infrequent with a high mortality rate and no response to steroid treatment [130].

Clinical and laboratory features

The diagnosis of PM/DM is based on the criteria described by BOHAN and PETER [131, 132]: 1) systemic muscle weakness; 2) increased serum muscle enzymes; 3) myopathic changes on electromyopathy; 4) typical histological findings on muscle biopsy; and 5) characteristic dermatological manifestations (heliotrope rash, periungual erythema, Gotton's papules and poikiloderma). Pulmonary involvement may precede by many years or occur simultaneously, or follow the muscular manifestations [133].

Four main types of clinical presentations of ILD associated with PM/DM have been reported: 1) acute presentation (<2 weeks) with fever, dyspnoea and lung infiltrates; 2) insidious onset of dyspnoea, cough and lung infiltrates; 3) asymptomatic pulmonary infiltrates without respiratory symptoms; and 4) abnormal PFTs and HRCT with normal chest film [134]. No correlation has been found between the extent and severity of the muscle or skin disease and the development of ILD [135]. Arthritis is more common in PM/DM with ILD [118, 119].

Radiological features

The CT patterns of lung involvement associated with HRCT in PM/DM vary widely among patients [136]. There are many types of radiographic abnormalities on HRCT, including parenchymal micronodules and nodules, linear opacities, irregularity of the interfaces between peripheral pleura and aerated lung parenchyma, ground glass opacities, honeycombing and traction bronchiectases or bronchiolectases [124, 126, 127, 137]. These findings were localised predominantly in the pulmonary lower zones. Studies have shown that NSIP is the most common form of ILD [3, 106, 124]. In one of the aforementioned studies, DOUGLAS *et al.* [124] scrutinised HRCT findings in 30 patients with PM/DM, of whom 22 underwent a surgical lung biopsy. They observed the following: consolidation in 53%, irregular linear opacities in 43%, ground glass opacities in 43%, pleural effusions in 20%, and no honeycombing in any patients. The above features were seen in 18 cases of NSIP, two cases of DAD, and one case each of UIP and OP [124]. ARAKAWA *et al.* [137] reported similar results in 14 cases of PM/DM with histologically proven NSIP. Consolidation is also a regular finding in other studies [138, 139]. Although there was no histological confirmation, it was suggested that these findings correlated with an OP. Often patients with PM/DM have both NSIP and OP. Rarely, LIP and UIP are found in PM/DM [3]. One more manifestation of PM/DM is a sudden respiratory decompensation, as seen in AIP. The radiological features of this, which correspond to the histological findings of DAD, are extensive ground glass opacities and consolidation, with no subpleural predominance [138].

Bronchoalveolar lavage

There are few reports that have included data about the BAL cell profiles in PM/DM patients with ILD. However, BAL cell differential may be a helpful prognostic indicator in PM/DM patients with ILD. Patients with ILD had poor outcome when the initial BAL showed neutrophilic alveolitis [119].

Lung biopsy

Lung biopsy has no diagnostic value for PM/DM, but the histological appearance was useful for determining the prognosis under treatment [129]. In PM/DM, NSIP is much more frequent than a UIP, OP or LIP pattern [124]. Patients with OP have a more favourable prognosis than those with UIP, and patients with DAD have a uniformly poor prognosis [119, 129, 140–143].

Serum biomarkers

Antisynthetase antibodies are detected in 40–80% of patients with PM and ILD (anti-Jo1 being the most frequent) [119, 124, 144, 145]. Anti-Jo1 is present in 23% of all patients with PM. SP-D serum levels have been found to be higher in patients with PM/DM and ILD compared with patients without lung involvement and healthy controls [146]. Similarly, serum levels of KL-6, a glycoprotein expressed on type-II alveolar pneumocytes and bronchial epithelial cells, have been found to be increased in PM/DM patients with interstitial lung involvement when compared with patients without parenchymal disease and healthy controls [147]. Finally, SP-D is suggested to be a useful marker in patients with PM/DM [146].

Treatment

Corticosteroids, either oral or *i.v.*, are used as initial treatment (prednisone 40–60 $mg \cdot day^{-1}$) [148]. Patients failing to respond to corticosteroids should be treated with cytotoxic agents [144]. Although data are limited to small series and case reports, responses have been noted with cyclophosphamide, azathioprine, MTX, cyclosporine A and racrolimus, even in patients failing to respond to corticosteroids [148]. Although useful in refractory PM, *i.v.* immunoglobulins have not been evaluated for their effect on lung involvement [149].

SYSTEMIC LUPUS ERYTHEMATOSOUS

SLE is as autoimmune disease characterised by disturbances in innate and adaptive immune mechanisms. SLE primarily affects females. Multiple systems and organs may be involved. Tissue damage and dysfunction are mediated by autoantibodies and immune complex formation. The respiratory system is frequently

involved by the disease and respiratory involvement is more common in males than in females. Pulmonary manifestations usually occur in patients with multisystem disease and include pleural involvement, parenchymal disease, atelectasis, pulmonary vascular disease, diaphragmatic dysfunction and upper airway dysfunction [150]. The pulmonary manifestations may range from subclinical abnormalities to life-threatening disorders. Many of these manifestations are seen in the antiphospholipid syndrome (APS) as well as in both the primary and secondary syndrome. The catastrophic APS may affect the lung in up to 66% of cases and may present with acute respiratory distress syndrome, pulmonary embolism, pulmonary artery thrombosis, *in situ* microthrombi, or even with alveolar haemorrhage [151]. Moreover, cases in which APS presentation was associated with fibrosis and/or alveolitis have been reported. However, the prevalence and severity of ILD in SLE is considerably lower than that in other CVDs.

Clinical features

The diagnosis of SLE is based on the criteria of the American College of Rheumatology, which were updated in 1997 [152]. Although lung involvement is not a criterion for SLE diagnosis, lung involvement has been associated with increased mortality [153, 154].

Acute lupus pneumonitis is an uncommon manifestation of SLE affecting 1.4–4% of patients. The typical manifestations include dyspnoea, cough fever, pleuritic pain and possible haemoptysis. Pulmonary haemorrhage is a rare but life-threatening manifestation occurring in <2% of SLE patients. It carries a poor prognosis with mortality rates of 70–90%.

Diffuse ILD is relatively uncommon in SLE, although it may dominate the clinical picture in some patients. This involvement of the lung affects 3–8% of SLE patients. The onset may be insidious, with a chronic nonproductive cough, dyspnoea on exertion and recurrent pleuritic pain.

Radiological features

Initial studies suggested a very low incidence based on chest radiography [74]. However, two HRCT series have demonstrated a higher rate of ILD features. FENLON *et al.* [155] have found evidence of ILD in one third of patients with SLE, although the majority of them were classified as mild involvement. Only two of the 34 patients included in the study had honeycombing [155]. Moreover, BANKIER *et al.* [156] also found pulmonary fibrosis in one third of 45 asymptomatic SLE patients, confirming the ability of HRCT to demonstrate subclinical disease. Importantly, in both reports, interlobular septal thickening was the most frequent interstitial abnormality. Moreover, no correlation has been found between HRCT appearances and symptoms, disease duration, double-stranded DNA titres, smoking history or nonpulmonary involvement in a prospective study of 29 SLE patients [157]. However, the authors observed unusually prevalent HRCT appearances suggestive of ILD in patients with SLE, suggesting that subclinical lung disease is common [157].

Although acute lupus pneumonitis and pulmonary alveolar haemorrhage are histopathologically distinct, the imaging features are similar and distinguishing between them can be difficult. Bilateral airspace opacification (consolidation and ground glass opacities) are found in both conditions [74]. Rapid resolution of radiological changes may favour pulmonary haemorrhage, whereas acute lupus pneumonitis may be accompanied by pleural effusions [74]. The chest radiography and CT scans of acute lupus pneumonitis show uni- or bilateral alveolar infiltrates which usually predominate in the lower lobes. LIP has been described in a few patients with SLE [74]. In these cases, the development of lung cysts should suggest the diagnosis of LIP [158–160]. Finally, the clinicoradiological syndrome of OP characterised by patchy alveolar infiltrates has been described in patients with SLE [161–163].

Bronchoalveolar lavage

In patients with both SLE and APS a lower than normal CD4+/CD8+ ratio in BAL was seen, suggesting subclinical ILD in patients who were asymptomatic regarding respiratory symptoms [164].

Lung biopsy

Acute lupus pneumonitis is characterised by DAD microscopically, whereas in pulmonary alveolar haemorrhage a neutrophilic capillaritis is the pathological hallmark [165]. In chronic interstitial pulmonary disease of SLE, histological reports describe nonspecific abnormalities with interstitial lymphocytic infiltrates, interstitial fibrosis and honeycomb changes [166, 167]. The incidence of NSIP in SLE is not well defined [106]. Nevertheless, available evidence indicates that the pulmonary fibrosis shown by HRCT in SLE is most in keeping with NSIP pattern [74]. It seems likely that a proportion of these patients may have developed fibrosis following an initial lupus pneumonitis.

Serum biomarkers

Lung involvement does not correlate with any biological marker, although in one study an association between anti-SS-A antibodies and chronic IP has been observed [168]. However, this observation was not confirmed in later studies, which described only an association between low $D_{L,CO}$ and anti-U1 ribonucleoprotein (RNP) antibodies [169].

Treatment

Acute lupus pneumonitis, which is often accompanied by capillaritis with diffuse alveolar haemorrhage, is often a lethal pulmonary complication of SLE with a mortality rate >50% [170]. It is crucial to start treatment of life-theatening haemorrhage promptly. Although there is lack of controlled studies for the treatment of acute lupus pneumonitis and diffuse alveolar haemorrhage, the current recommendations are based on case reports and clinical experience. Preferred treatment is pulse methylprednisolone (1,000 $mg \cdot day^{-1}$ for three consecutive days) alone or in combination with pulse or oral cyclophosphamide [171]. Corticosteroids and immunosuppressive drugs are routinely used to treat UIP, NSIP, OP and LIP in patients with SLE, although the effectiveness of these therapies has not been verified by controlled trials.

MIXED CONNECTIVE TISSUE DISEASE

MCTD was first described in 1972 as a distinct overlap characterised by features of systemic SSc, SLE and PM/DM, with respiratory involvement occurring in 80% of patients [172].

A prerequisite for the diagnosis of MCTD is the presence of high titres of antibodies against uridine-rich RNA-small nuclear RNP (anti-RNP) [173].

Clinical features include a high frequency of Raynaud's syndrome, swollen hands, sclerodactyly, arthritis, PM and ILD [174]. The major respiratory manifestations include ILD and pulmonary fibrosis (20–65%), pleural effusion (50%) and pulmonary hypertension (10–45%). Other pulmonary disorders are pulmonary vasculitis, pulmonary thromboembolism, pulmonary infections (secondary to aspiration pneumonia due to oesophageal motility alterations and immunosuppression), alveolar haemorrhage, pulmonary nodules, pulmonary cysts, mediastinal lymphadenopathy and respiratory muscle dysfunction.

Given that the clinical features of the condition include aspects of all the above disorders, a spectrum of radiological features might be expected. However, the HRCT features of MCTD are not extensively studied. In one study of 41 patients, abnormalities were common with ground glass attenuation found in all patients, while nodules and reticular opacities were also frequently seen, predominantly in the peripheral lower zones [175]. Honeycombing was less common. Overall, the authors commented that the appearances were similar to that of NSIP and UIP. It is interesting to note that no cases of mosaic attenuation were found, and other signs of airways disease were less frequently observed than in, for example, RA. As with SSc, proximal pulmonary artery enlargement due to pulmonary hypertension, as well as oesophageal abnormalities, are found in MCTD [176]. Pleural effusions and pleural thickening are also seen, which resembles SLE [154].

The most frequent causes of death in patients with MCTD are pulmonary hypertension (26.1%), respiratory insufficiency (23.2%) and heart failure (15.9%) [177]. Thus, the cause of death in MCTD patients is quiet different from those of SLE and SSc patients [178, 179]. Pulmonary hypertension has not been demonstrated to be the primary cause of death in either SLE or SSc patients. The prevalence of pulmonary hypertension in MCTD patients has been reported as 4% [180, 181].

As in other CTD, there are no controlled data on which to base the therapy for interstitial lung involvement in MCTD. In general, most disorders are treated with corticosteroids and/or immunosuppressive agents, which are directed against the autoimmune-driven mononuclear cell infiltration in the lung parenchyma. Interstitial fibrosis is irreversible but treatment may be warranted, primarily in the hope of preventing or slowing down its progression. Regimens used for IP in SSc appear appropriate and usually consist of low-dose corticosteroids in combination with cyclophosphamide or azathioprine [182, 183].

CONCLUSIONS

Interstitial lung involvement is common and potentially life-threatening in CVDs. Every patient with CTD deserves a thorough work-up, in order to be investigated whether lung involvement is present, and if so, to what degree. Routine checking includes clinical evaluation, lung function and clinical exercise tests, imaging modalities, BAL, lung biopsy, and use of some serum biomarkers, like KL-6 and SP-D. Early detection of pulmonary involvement is very important for the initiation of a targeted therapy, because the damage to the lung parenchyma may be already irreversible at the time of the onset of respiratory symptoms.

HRCT is less useful in the key distinction between subclinical and clinically significant disease. No cut-off for disease extent exists at which it can be concluded that the illness has become clinically important. Informal evaluation of the extent of disease on HRCT is a useful exercise because abnormalities are clearly limited or clearly extensive in the majority of cases. However, in the remaining cases, it is necessary to base judgements of disease severity on pulmonary function evaluation (especially $D_{L,CO}$). The introduction of treatment for ILD in CTD requires the clinician to discriminate between ''reversible'' disease, in which a response is expected and high-dose therapy is often warranted, and fibrotic disease, in which long-term treatment is used to slow or prevent progression of disease. HRCT is prognostically useful in CTD, usually for the identification of a minority of cases in which appearances are likely to be reversible. Although the radiation dose associated with CT is low with interspaced HRCT protocols, patients with CTD are, on average, younger than those with IIPs, and clinicians should properly perform CT as frequently as it is necessary. Moreover, pulmonary function trends are helpful in many cases, whether disclosing stability or disease progression, and the additional information known by serial HRCT is unlikely to refine management. BAL is advocated for its role in excluding other causes of parenchymal involvement in CTD, *e.g.* infections, drug reactions and capillaritis with diffuse alveolar haemorrhage. Therefore, the decision of whether to treat is a challenging one, and should be based on evaluation of disease severity (on the basis of CT extent and lung function) and longitudinal disease behaviour. Recent advances in scleroderma lung clearly showed that treatment effect amounts largely to the prevention of progression of fibrotic disease. However, because of the significant toxicity of cyclophosphamide, the assessment of alternative, less toxic, immunosuppressive agents for the long-term management of SSc-associated ILD is needed.

The final conclusion is that every patient with collagen vascular disease should be thoroughly evaluated for lung involvement and, *vice versa*, in every diffuse interstitial lung disease pattern a connective tissue disorder should be investigated.

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