Ple slices through the lung, from top (apex) to bottom (base), and can even detect lung involvement in early phases when no symptoms are present. 99mT-DTPA is recommended in those patients with isolated diffusion deficits on lung function tests and in addition to HRCT in confirming the suspicion of vascular disease rather than early fibrosing alveolitis. Bronchoscopy with BAL is an invasive test that also may provide information about the inflammatory status of the affected areas of the lung detected during HRCT. In order to detect alveolitis, it should be performed as early as possible, to start prompt immunosuppressive treatment.

Keywords Systemic sclerosis • Interstitial lung disease

Lung involvement frequently complicates systemic sclerosis (SSc), provoking loss of quality of life and a poor expectation of survival. For this reason an early diagnosis of lung involvement is warranted: high-resolution computed tomography (HRCT), pulmonary function tests (PFT), lung scintigraphy with DTPA and bronchoalveolar lavage (BAL) are mandatory to define and follow-up pulmonary interstitium. Coughing and a sensation of breathlessness on exertion are the earliest symptoms of lung involvement. Lung involvement may be investigated with PFTs, which are non-invasive and require breathing into a tube via a mouthpiece. Forced vital capacity, which measures the total amount of air capable of being blown forcefully, and the diffusion capacity for carbon monoxide, a measure of how well oxygen diffuses into blood, are the most important functional measures. A routine chest X-ray may demonstrate fibrosis, but it is not very sensitive for detecting early or mild disease. For this reason, a HRCT scan is required. This non-invasive investigation provides images of multiple slices through the lung, from top (apex) to bottom (base), and can even detect lung involvement in early phases when no symptoms are present. 99mT-DTPA is recommended in those patients with isolated diffusion deficits on lung function tests and in addition to HRCT in confirming the suspicion of vascular disease rather than early fibrosing alveolitis. Bronchoscopy with BAL is an invasive test that also may provide information about the inflammatory status of the affected areas of the lung detected during HRCT. In order to detect alveolitis, it should be performed as early as possible, to start prompt immunosuppressive treatment.

Keywords Systemic sclerosis • Interstitial lung disease

Pulmonary involvement is the leading cause of morbidity and mortality in systemic sclerosis (SSc) patients [1]. This condition may occur in patients both with diffuse (dSSc) and limited (lSSc) cutaneous disease. Basilar interstitial fibrosis is present at post mortem in up to 75% of SSc patients [2]. The earliest description of the pathology of SSc interstitial lung disease (ILD) derives from post mortem studies, suggesting that the primary histopathologic finding is interstitial fibrosis with honeycombing [3]. The temporal and causative relationship between the events of ILD is unclear. Alveolitis, membrane thickening and/or the modification of microvascular structure are the main hallmarks of lung involvement that may lead, with the progression of the disease, to ILD and to pulmonary arterial hypertension.

The presence of specific autoantibodies, especially anticientromere (ACA) or anti-SC1 70, has been shown to correlate with the presence of pulmonary parenchymal and vascular abnormalities in SSc patients. It has been suggested that ILD is less frequent in SSc patients with ACA than in those without this antibody, but this has not been
confirmed [4]. Furthermore, single-breath carbon monoxide diffusing capacity (DLCO) has been shown to be lower in SSc patients with anti-SC1 70 antibodies than in patients without anti-SC1 70, suggesting a greater incidence of interstitial disease in this group [5].

**Pathology**

The interstitium is defined as the alveolar walls (including epithelial cells and capillaries), septae and the perivascular, perilymphatic and peribronchiolar connective tissue. Idiopathic interstitial pneumonias are characterised by expansion of the interstitial compartment by inflammatory cells and fibrosis occurs in many cases. According to the American Thoracic Society/European Respiratory Society consensus, idiopathic interstitial pneumonias are classified into clinicopathologic entities based on histopathology, but depend on the close interaction of clinician, radiologist and pathologist. Six distinct subgroups are distinguished: usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), desquamative interstitial pneumonia, acute interstitial pneumonia, cryptogenic interstitial pneumonia and lymphoid interstitial pneumonia [6]. Histopathologic classification plays a key role in separating multiple forms of idiopathic interstitial pneumonia into clinically meaningful categories with important differences in natural history, prognosis and treatment. UIP defines idiopathic pulmonary fibrosis and is the most common form of idiopathic interstitial pneumonia; it has distinctive morphologic features that allow precise diagnosis in classical cases. The other categories differ from UIP but the histopathologic findings do not, by themselves, allow specific diagnosis in most cases, and a careful correlation with clinical and radiologic findings is required [7].

NSIP is the most common histopathologic pattern found in SSc lung, although UIP can be present [8]. In fact, in surgical lung biopsies of 80 SSc patients, 62 NSIP, 6 UIP, 6 unclassifiable end-stage fibrosis, 4 respiratory bronchiolitis and 1 organising pneumonia have been found [9].

NSIP is characterised by the presence of varying degrees of inflammation and fibrosis within the alveolar walls: most biopsy samples contain either inflammation with minimal fibrosis or a mixture of inflammation and fibrosis, though a few are composed mainly of fibrosis with minimal inflammation. The process may be patchy with intervening areas of unaffected lung, but the changes are temporally uniform: they usually occur over a single, relatively narrow time span [10]. In UIP fibrosis predominates over inflammation. “Fibroblast foci” represent microscopic zones of acute lung injury set against a background of chronic scarring, contributing to the variegated appearance or temporal heterogeneity of UIP. They are randomly distributed within areas of interstitial collagen deposition and consist of fibroblasts and myofibroblasts arranged in a linear fashion within a pale-staining matrix. Fibroblast foci are not specific for UIP, but they are invariably present and therefore represent an important diagnostic criterium [7].

Patients with NSIP have better prognosis than those with UIP [11]. Unfortunately, fibrotic NSIP can be difficult to distinguish from UIP, as both patterns can be seen in multiple biopsies from the same patient; even in multiple biopsies from the same lobe [12].

**Clinical features**

Dyspnoea on exertion, hypoxaemia and non-productive cough are the most common manifestations of pulmonary fibrosis even in patients without radiological evidence of pulmonary damage. Haemoptysis can also be observed in advanced fibrosis. Fine bibasilar crackles at chest auscultation are characteristic. Increased and palpable pulmonary component of the second heart sound, right ventricular gallops, murmurs of pulmonary and tricuspid insufficiency, jugular distension, hepatojugular distension and feet oedema can reflect signs of pulmonary hypertension.

**Diagnosis**

*Chest X-ray*

Chest X-ray detects lung volumes, distribution of infiltrates, pleural disease and lymphadenopathy; 10% of symptomatic patients may have a normal chest radiograph, as chest X-ray has a low sensitivity for early lung involvement.

*Pulmonary function test (PFT)*

Restrictive ventilatory defects are the most common findings in patients with SSc [13]. However, by the time these defects are diagnosed on spirometry, pulmonary disease is fairly advanced. A reduction in DLCO is reportedly an early sign of pulmonary disease in SSc, as well as an important predictor of mortality [14]. Even so, diffusion across the alveolar capillary units may be altered by parameters other than interstitial fibrosis.

A high percentage of SSc patients with abnormal DLCO have been observed with or without a decrease in forced vital capacity (FVC); the reduction of DLCO alone may also suggest the presence of pulmonary hypertension [15]. Assessment of PFT is recommended in SSc as chest radiography or respiratory symptoms cannot predict early lung involvement. It has been observed that 62% of the patients reached an FVC of <55% of the predicted value in the first 5 years after the onset of their very first SSc symp-
this consistent with another study, which confirmed the presence of an abnormal FVC early in the disease is one of the most important risk factors for the development of end-stage ILD [17]. Thus, in the first 5 years of disease, patients should have PFT monitored closely every 6 months until lung function stabilises.

High-resolution computed tomography (HRCT)
Chest HRCT is the non-invasive gold standard technique for the diagnosis of SSc ILD. HRCT is recognised as a sensitive tool for predicting the histological characteristic of the lung parenchymal abnormalities, in patients with idiopathic pulmonary fibrosis. It allows imaging of the lung parenchyma in remarkable detail that suggests its weight in the diagnosis of fibrosing alveolitis, providing a non-invasive alternative to open lung biopsy. Ground glass opacification indicates alveolitis leading eventually to lung fibrosis and honeycombing [18]. HRCT abnormalities indicative of ILD have been documented in more than 85% of SSc patients: also in cases with abnormal chest X-ray, HRCT was a more sensitive detector of the extent or severity of interstitial involvement [19]. In patients with pulmonary fibrosis, the cell population in the BAL fluid, from different lung sections, is not uniform, and HRCT scanning appears to be a useful method to identify pulmonary areas with different inflammatory activity [20]. Typical interstitial abnormalities identified on HRCT include thickened interlobular septa, subpleural cysts and honeycombing lung formation. Additional findings may include subpleural micronodules, small airway ectasia (bronchiectasis and bronchiolectasis) and ground glass opacification [21]. Ground glass opacification on HRCT correlates with the presence of air space inflammation in the lung (alveolitis) and decreased DLCO [20]. CT patterns of lung disease in patients with SSc have been compared to biopsy-proven idiopathic NSIP and idiopathic pulmonary fibrosis: the pattern of lung involvement at HRCT in SSc patients is different from that in idiopathic pulmonary fibrosis. In fact, in SSc, fibrosis is less coarse and the proportion of ground glass opacification is greater than that in patients with idiopathic pulmonary fibrosis. The HRCT features of lung disease in SSc closely resemble those in patients with NSIP and are in agreement with recent observations that NSIP is the most prevalent pattern at histopathologic examination [22].

HRCT should be enclosed in the variables to be used in studies specifically devised to address lung involvement for qualitative assessment (normal/ground-glass/fibrosis) or semi-quantitative assessment (Wells’ or Warrick’s scoring systems).

Technetium diethylene-triamine-pentacetate (DTPA) radionuclide scanning
Clearance of inhaled ⁹⁹ᵐT-DTPA is an index of lung epithelial permeability [23]. Increased ⁹⁹ᵐT-DTPA clearance may be a sensitive marker of inflammation and normal clearance certifies absence of inflammation [24]. A study of ⁹⁹ᵐT-DTPA in a heterogeneous group of patients with idiopathic pulmonary fibrosis showed that normal ⁹⁹ᵐT-DTPA clearance selects patients with favourable prognosis [25]. Rapid clearance of ⁹⁹ᵐT-DTPA can be useful in patients with an isolated reduction in DLCO to differentiate between those with early fibrosing alveolitis from those with pulmonary vascular disease [26]. A recent study demonstrated that clearance of inhaled ⁹⁹ᵐT-DTPA is of no value in following the progress of idiopathic pulmonary fibrosis [27]. Based on the evidence, ⁹⁹ᵐT-DTPA is recommended in those patients with isolated diffusion deficits on lung function tests in addition to HRCT in confirming the suspicion of vascular disease rather than early fibrosing alveolitis.

Bronchoalveolar lavage (BAL)
BAL is a diagnostic technique that yields insights into immunologic, inflammatory and infectious processes occurring at the alveolar level. Changes in the relative and absolute number of cells in BAL fluid have been described in a variety of lung diseases. In BAL fluid obtained from healthy, non-smoking adults without lung disease, few lymphocytes (6.80±1.80%), neutrophils (0.50±0.50%) and eosinophils (0.10±0.06%) are found, while the predominant cells are macrophages (92.60±1.60%).

A variety of cell types are increased in BAL fluid from SSc patients with pulmonary involvement, including alveolar macrophages, CD8 T cells, mast cells, basophils, eosinophils and neutrophils. In idiopathic pulmonary fibrosis a higher percentage of lymphocytes and neutrophils on BAL has been shown to predict those patients more likely to respond to immunosuppressive treatment [28]. A link between the presence of alveolitis at baseline and the subsequent loss of FVC in a small cohort of patients has been observed [29]; a more recent work has confirmed these findings suggesting that the presence of active alveolitis may be used to predict future loss of FVC [30]. A significant and direct correlation between the extent of disease seen on HRCT and the percentage of neutrophils and eosinophils on BAL has been demonstrated, suggesting that greater radiologic evidence of disease seen on lung tissue should correlate with more intensive alveolitis [31]. However about 50% of SSc patients with normal HRCT had abnormal cellularity observed by BAL [20]. A recent study investigated the concordance of findings on HRCT and BAL when the findings of both techniques involved the same lobe [32]. The findings of this study suggest that in addition to HRCT, BAL, differential cell counting and culture from at least 2 segments of lung should be performed for diagnosing SSc alveolitis as HRCT did not detect all sites of inflammation and did not identify infectious aetiologies. BAL allows identification of the kind and entity of the inflammatory process, and the
different type of alveolitis, which may play a crucial role in the clinical progression of fibrosing alveolitis in SSc. In alveolitis BAL may be a guide to prognosis and to the choice of treatment.

In order to detect the inflammatory process in the alveolar wall, BAL should be performed as early as possible, even when the DLCO and CT scan are negative in order to start a prompt immunosuppressive treatment.

Thoracoscopic lung biopsy
Although it is considered the gold standard in the diagnosis of fibrosing alveolitis, the role of thoracoscopic lung biopsy is controversial. Both patterns NSIP and UIP can be seen in multiple biopsies from the same patient, even in multiple biopsies from the same lobe [12] and there is significant interobserver variability even among expert histopathologists in the recognition of these entities [7]. For this reason, thoracoscopic lung biopsy might be indicated when diagnosis remains questionable after review of the clinical, physiologic, radiographic and bronchoscopic data.

Markers of lung disease
KL-6, a glycoprotein antigen expressed mainly on type II pneumocytes in alveoli and respiratory bronchiolar epithelial cells [33], KL-6 concentrations are elevated in the sera from patients with ILD [34]. Recent studies have shown that serum KL-6 concentrations are increased in SSc patients with pulmonary fibrosis compared to those without [35]. Furthermore, increased serum levels of KL-6 are associated with the presence and extension of pulmonary fibrosis on HRCT and inversely correlated with FVC, DLCO and response to therapy [36].

Surfactant protein (SP) belongs to the collectin subfamily of the CC-type lectin superfamily [37] and is produced and secreted by alveolar type II pneumocytes in alveoli [38]. Increased serum SP concentrations were detected in patients with ILD, including idiopathic interstitial pneumonia and pneumonia in SSc [39, 40]. A recent study has shown that SP was a more sensitive marker for pulmonary fibrosis than KL-6 in SSc. By contrast KL-6 showed higher specificity than SP [41]. Serum levels of pulmonary and activation-regulated chemokine were recently found to correlate with pulmonary fibrosis and reflect more sensitively fibrosis activity than serum KL-6 or SP-D levels in SSc do [42].

Combined use of these markers with the other laboratory findings described above should be helpful to diagnose and monitor the activity of pulmonary fibrosis in SSc.

Exhaled nitric oxide (NO) is derived from the upper and lower respiratory tract. Measurement of NO in exhaled air has been used increasingly to assess the potential role of endogenous lung NO in a variety of disease states [43]. Several studies have reported an increase in exhaled NO concentrations among patients with ILD associated with SSc [44–46]. Lower exhaled NO values have been reported in patients with SSc with pulmonary hypertension [44], whereas elevated levels were also found in ILD without pulmonary hypertension [45]. It has been demonstrated that exhaled NO is not elevated in patients with SSc and ILD and pulmonary hypertension but is significantly higher in patients with SSc without ILD [47]. This may reflect subclinical inflammation in these patients. An abnormality in BAL cytology in patients with PSS without ILD supports this assertion. This suggests that exhaled NO may be a sensitive non-invasive marker of early pulmonary inflammation [47].

Conclusions
ILD frequently complicates SSc, provoking loss of quality of life and a poor expectation of survival. For this reason early diagnosis of lung involvement is warranted. HRCT, PFT, lung scintigraphy with DTPA and BAL are mandatory to define and follow-up pulmonary interstitium and microvasculature [48].

The clinical course of ILD is variable and requires an adequate baseline assessment and systematic monitoring, as outlined in Fig. 1. Additional investigations required at baseline include PFT and CXR. Serial monitoring of PFT, particularly in the first 5 years after diagnosis, is crucial for the early identification of ILD. HRCT is indicated if PFT are abnormal at baseline or decline over time. BAL should be performed as early as possible, even when the DLCO and CT scan are negative for early diagnosis of ILD. DTPA scan may assist in the assessment of the patients with isolated diffusion reduction. A periodical evaluation is recommended to identify in due time morphological (CT) or functional (PFT) modifications (Fig. 1). In selected cases, lung biopsy may be suggested when diagnosis remains questionable after review of the clinical, physiologic, radiographic and bronchoscopic data. In conclusion, it is mandatory to start to treat SSc early, before organ damage occurs and to try to identify patients characterised by a rapid progression (diffuse acute subset).
these patients, appropriate treatment should be started to prevent deterioration of pulmonary function, improving the outcome of SSC.

References


O. Kaloudi et al.: Interstitial lung disease in systemic sclerosis