Difficulties in diagnosis of systemic sclerosis-related interstitial lung disease

Anniek Vrancken1, Ellen De Langhe2, Rene Westhovens2, Jonas Yserbyt1, Vincent Cottin3 & Wim Wuyts1

1Department of Pneumology, University Hospitals Leuven, Leuven, Belgium. 2Department of Rheumatology, University Hospitals Leuven, Leuven, Belgium. 3Department of Pneumology, Hospitals Louis Pradel, Claude Bernard Lyon 1 University Lyon, Lyon, France.

Keywords
Connective tissue disease, interstitial lung disease, systemic sclerosis, undifferentiated connective tissue disease.

Abstract
We discuss a case that demonstrates the difficulties in making a confident diagnosis of interstitial lung disease (ILD) associated with systemic sclerosis (SSc). Atypical symptoms can be present, suggesting the diagnosis of an underlying connective tissue disease (CTD), but it can take several years before a definite diagnosis can be made because there are insufficient features to fulfill the preset classification criteria (American College of Rheumatology criteria) for a definite underlying CTD. Close follow-up of these patients is necessary because patients with SSc-ILD have a poorer prognosis than those with SSc without pulmonary involvement. Treatment choice also differs between idiopathic ILD and SSc-related ILD.

Introduction
Connective tissue disease (CTD) is a heterogeneous group of systemic disorders that can affect any organ system. Interstitial lung disease (ILD) is the most common pulmonary manifestation, but airway/pleural or vascular pathologies and diffuse alveolar hemorrhage can also occur.

Although all systemic disorders are at risk for developing ILD, systemic sclerosis (SSc), rheumatoid arthritis, and polymyositis/dermatomyositis are more frequently associated with ILD [1]. Identification of an underlying CTD in these patients can be difficult because ILD can be the first or only manifestation of CTD.

Case Report
A 64-year-old Caucasian woman was referred because of a subacute onset of nonproductive cough and shortness of breath. Intermittently, she noticed slightly swollen and painful fingers but no morning stiffness or Raynaud’s phenomenon. Chest auscultation revealed fine bibasilar crackles. Lung function showed a restrictive pattern (total lung capacity 75%, forced vital capacity 80%) and a reduced diffusion capacity of carbon monoxide (DLco) of 60%. High-resolution computed tomography (HRCT) showed bibasilar consolidation with air bronchogram, reticular pattern, and ground glass opacities (Fig. 1). Antinuclear antibodies (ANA) were positive (1/640), nucleolar pattern although with negative subtyping, in the absence of anticentromere or Scl70 antibodies neither anti-neutrophil cytoplasmic antibodies, rheumatoid factor, nor anti-cyclic citrullinated peptide. Based on the HRCT imaging, the diagnosis of cryptogenic organizing pneumonia was made. The positive ANA and the presence of intermittently swollen fingers were suggestive of an underlying CTD; however, a firm diagnosis could not be made. All her complaints regressed without treatment during admission.
Two months later, the patient presented in the emergency room with recurrence of shortness of breath associated with decreased exercise capacity, dry cough, and arthralgia, without clinical signs of synovitis. A further decline in DLco to 42% was noted. Bronchoscopy with bronchoalveolar lavage was performed and revealed an increased eosinophil (14%) and neutrophil (10%) count without microbiological evidence of infection. A new HRCT showed increased bilateral ground glass opacities and consolidations in the lower lobes (Fig. 2), suggesting organizing pneumonia or nonspecific interstitial pneumonia (NSIP). ANA were unchanged with a titer of 1/640 (nucleolar pattern), once more without the identification of specific subclasses. Because no sufficient clinical signs of an underlying CTD were present, cryptogenic organizing pneumonia or idiopathic NSIP remained our preferred diagnoses although an underlying autoimmune disorder with NSIP could not be excluded. Therapy was refused by the patient because of spontaneous subjective improvement of symptoms.

Three years after the first presentation, she presented with thickening of the skin, hardening of the fingers, and Raynaud’s phenomenon. Nail-fold capillary microscopy showed not only a few giant capillaries and hemorrhages but also severe loss of capillaries with extensive avascular areas that was suggestive of SSC. Although serologic tests were not typical (only positive for ANA [1/160] but negative subtyping), the symptoms and findings (HRCT findings and low DLco [35%]) were now suggestive for the proposed diagnosis of SSC-associated ILD (SSc-ILD). An immunosuppressive treatment was proposed but refused by the patient because of stable DLco and the lack of respiratory symptoms.

**Discussion**

In this case report, a patient with ILD was followed for 3 years, with an initial diagnosis of cryptogenic organizing pneumonia or idiopathic NSIP. In spite of the positive ANA and signs of arthralgia, there were insufficient features to fulfill the preset classification criteria (American College of Rheumatology criteria) for a definite underlying CTD. This is also named undifferentiated CTD or ILD with autoimmune features [2]. After quite some time, a diagnosis of SSc-associated NSIP was made based on developing skin thickening and hardening with a suggestive capillaroscopy. In the early stage of SSc, Raynaud’s phenomenon, arthralgia, and soft-tissue swelling (“puffy” fingers) rather than skin thickening may be the most prominent features, suggesting the diagnosis of an underlying SSc, but it can take several years before a definite diagnosis can be made. Initially, there was no capillaroscopy performed. From a retrospective point of view, the diagnosis of SSc-ILD could maybe be made sooner if a capillaroscopy was performed earlier, according to the current criteria of early SSc [3]. Although this would not have made a difference in the treatment of this patient, earlier diagnosis could influence the treatment for other patients. Therefore, a systematic follow-up with a regular broad multi-organ evaluation is necessary because treatment choice and prognosis varies between idiopathic interstitial pneumonia and SSc-ILD.
Lung biopsies are not recommended for routine diagnosis of SSc-ILD, unless there are unusual clinical or radiological features. The pathologic and radiographic features of SSc-ILD are mostly those of NSIP or less commonly usual interstitial pneumonia. Patients with SSc-ILD have a better prognosis than those with idiopathic ILD [1, 2, 4].

The majority of patients with SSc-ILD have limited and stable disease and therefore not requiring treatment. However, a small group has a more severe and progressive course, necessitating initiation of immunosuppressive therapy to achieve and maintain remission [1]. First choice is intravenous cyclophosphamide based on two randomized controlled trials [5, 6], followed by maintenance treatment with either mycophenolate or azathioprine, as suggested by case reports and observational case studies [1, 2, 6]. There is no consensus about the dose of each intravenous pulse (range from 0.5 to 2 g·M\(^{-2}\)) or about the duration of therapy (generally 6–18 months). Further investigation is required to optimize the immunosuppressive therapy.

**Disclosure Statements**

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

**References**

1. De Lauretis A, Veeraraghavan S, and Renzoni E. 2011. Connective tissue disease-associated interstitial lung disease: how does it differ from IPF? How should the clinical approach differ? Chron. Respir. Dis. 8:53–82.
2. Gutsche M, Rosen GD, and Swigris JJ. 2013. Connective tissue disease-associated interstitial lung disease: a review. Curr. Respir. Care Rep. 1:224–232.
3. Avouac J, Fransen J, Walker UA, et al. 2011. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. Ann. Rheum. Dis. 70:476–481.
4. Bouros D, Wells AU, Nicholson AG, et al. 2002. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. Am. J. Respir. Crit. Care Med. 165:1581–1586.
5. Tashkin DP, Elashoff R, Clements PJ, et al. 2006. Cyclophosphamide versus placebo in scleroderma lung disease. N. Engl. J. Med. 354:2655–2666.
6. Hoyles RK, Ellis RW, Wellsbury J, et al. 2006. A multicenter, prospective, randomized, double-blind placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum. 54:3962–3970.