

Interstitial lung disease as the first manifestation of systemic sclerosis

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ABSTRACT

We describe three patients with progressive fibrosing interstitial lung disease (ILD) as the first and only manifestation of systemic sclerosis. In one patient the presence of anti-Scl-70 autoantibodies suggested systemic sclerosis to be the underlying cause of the disease. In the two other subjects, however, anti-Scl-70 antibodies were negative. In these patients the lung disease preceded other manifestations of systemic sclerosis by several years. Diagnosis, prognosis and treatment of systemic sclerosis-associated ILD is discussed.

KEYWORDS

Interstitial lung disease, scleroderma sine scleroderma, systemic sclerosis

INTRODUCTION

Idiopathic interstitial pneumonia (IIP) comprises a group of disorders of unknown aetiology, histopathologically characterised by a variable pattern of inflammation and/or fibrosis of the pulmonary interstitium. Various clinical entities, each of which defined by a specific histopathological pattern, are recognised.¹ Idiopathic pulmonary fibrosis (IPF) and (fibrotic) nonspecific interstitial pneumonia (NSIP) account for approximately 80% of IIP cases.¹ Histopathologically, IPF is characterised by a usual interstitial pneumonia (UIP) pattern and NSIP by a nonspecific interstitial pneumonia pattern.²⁻⁶ The histopathological hallmark of UIP is the heterogeneous appearance at low magnification with alternating areas of normal lung, interstitial inflammation, fibrosis and honeycomb

changes. Moreover, characteristic foci of proliferating fibroblasts are a consistent finding. In contrast, the main histopathological feature of NSIP is the homogeneous appearance of either inflammation (cellular type NSIP) or fibrosis (fibrotic type NSIP). Although the process may be patchy with intervening areas of unaffected lung, the observed changes in NSIP are temporally uniform. Although the prognosis of both forms of IIP is still poor, the prognosis in fibrotic NSIP patients is significantly better than in IPF.³⁻⁶ Interstitial lung diseases, histopathologically indistinguishable from IIP, can also be observed as pulmonary manifestation of various collagen vascular diseases (CVD).⁷ In most of these patients a fibrotic NSIP pattern is observed; however, a UIP pattern can also be present.^{8,9} The incidence of interstitial lung disease (ILD) differs among the various CVD. In systemic sclerosis, it can be observed in the majority of patients during the course of the disease¹⁰ whereas, in systemic lupus erythematosus it is observed in a minority of patients only.¹¹ Moreover, in some CVD, ILD may be the first manifestation of the disease. In particular, in patients with polymyositis dermatomyositis and rheumatoid arthritis, the interstitial lung disease may precede the other manifestations by several years.^{7,12,13} Interstitial lung disease as a first manifestation of disease in systemic sclerosis, however, is extremely rare, and was previously reported to be associated with the presence of autoantibodies against topoisomerase I (anti-Scl-70 antibodies).¹⁴⁻¹⁶ In most cases of systemic sclerosis, however, lung involvement is observed relatively late in the course of the disease.^{10,16,17} In this paper we describe three patients with ILD as the first manifestation of disease in systemic sclerosis. Moreover, diagnosis, prognosis and treatment of systemic sclerosis-associated ILD are discussed.

CASE REPORTS

Case 1

A 59-year-old man was admitted to our hospital in 1999 because of sudden onset chest pain and high fever. He also suffered from progressive dyspnoea on exertion that had started two months prior to admission. He was a nonsmoker and he had no previous history of documented lung disease. On physical examination, Velcro-like crackles were heard at both lung bases; he showed no signs of heart failure. Physical examination was otherwise unremarkable.

Laboratory tests revealed an erythrocyte sedimentation rate of 70 mm within the first hour; antinuclear factor (ANF) was positive, while anti-DNA antibodies were absent.

Chest X-ray revealed signs of increased interstitial attenuation. Contrast-enhanced computed tomography (CT) revealed a pulmonary embolism in the left upper lobe. High resolution (HR) CT confirmed the presence of a bilateral interstitial lung disease with ground glass attenuation. He was treated with intravenous heparin and broad-spectrum antibiotics. Sputum and blood cultures remained negative. By serology, viral and atypical infections were excluded. HIV infection was also ruled out.

At that stage, anti-Scl-70 antibodies turned out to be positive. So, a diagnosis of a fibrosing ILD (probably NSIP) of unknown origin was made; in view of the anti-Scl-70 antibodies, however, the most likely diagnosis was systemic sclerosis sine scleroderma. He was treated with corticosteroids (prednisone 1 mg/kg), whereupon his clinical condition gradually improved. After discharge, during follow-up at the outpatient clinic over the next three months, his hands became diffusely swollen and the skin thickened. He developed Raynaud's phenomenon, started to complain about difficulties in swallowing food and showed signs of sclerodactyly. On the chest X-ray, the ILD was progressive. Taken together, the diagnosis of limited scleroderma was made with ILD as its first manifestation. Because of progression of the ILD, he was additionally treated with azathioprine and has been stable since.

Case 2

In 1998 the second patient, a female from Afghanistan aged 32 years, was referred to our hospital for further evaluation of a gradually progressive ILD. Her clinical history started in 1996. A chest X-ray, which was performed because of nonspecific, short-lasting right-sided knee pain, revealed diffuse interstitial abnormalities in both lungs. The patient was an active smoker but did not have any pulmonary symptoms. During the wintertime, however, she had complaints suggestive of Raynaud's phenomenon.

Already in 1996, HR-CT revealed a fibrosing ILD with reticular abnormalities with traction bronchiectasis and ground glass attenuation with a lower lobe predominance (figures 1 and 2). During follow-up, progression of disease

Figure 1. High-resolution computer tomography at the carina level in case 2



Aspecific parenchymal destruction in the right mid zone. Fine reticular opacities with a subpleural localisation and subtle ground glass attenuation of the lung parenchyma at the left side.

Figure 2. High-resolution computer tomography at the lung base in case 2



Marked reticular abnormalities with traction bronchiectasis and diffuse ground glass attenuation.

was documented, and she started to suffer from shortness of breath. Pulmonary function tests showed decreased lung volumes and a decreased carbon monoxide diffusion capacity. A video-assisted thoracoscopic lung biopsy was performed. The biopsies showed a UIP pattern, so the clinical diagnosis of IPF was made. Infection, including tuberculosis, was ruled out. At that time, besides the possible Raynaud's phenomenon, there were no clinical signs of any systemic disease. She was treated with high-dose intravenous methylprednisolone. Her symptoms decreased and both radiologically, as well as functionally, a significant improvement was observed. She was subsequently treated with a maintenance dose of 10 to 20 mg of prednisone daily and was stable over the next four years. Because of the

Raynaud's phenomenon and her young age, we were aware of the fact that a CVD might be the underlying cause of the ILD. Rheumatoid factor was positive (20 kU/l), however, antinuclear antibodies (ANA), anti-Scl-70 and anticentromere antibodies (ACA) were repeatedly negative. In 2003, almost five years after the initial presentation, more clinical signs of systemic sclerosis appeared. Her skin thickened, she developed telangiectasias and she started to complain about stiffness of her hands, which became diffusely swollen. She developed sclerodactylia and passage problems of the oesophagus. After being stable for several years, also the pulmonary symptoms increased, and both lung function tests as well as HR-CT scanning showed progression of disease. She was treated with intermittent intravenous cyclophosphamide, and has been clinically stable since. Upon treatment with cyclophosphamide the swelling of her hands disappeared. In 2005, nine years after the initial presentation, anti-Scl-70 antibodies were detected for the first time.

Case 3

The third patient, a 35-year-old female from Morocco, was referred to our hospital in 1998, with coughing and shortness of breath, which she had been suffering from for the last four years. On physical examination, Velcro-like crackles were heard over both lung bases. Chest X-ray revealed interstitial abnormalities as well as bronchiectases. HR-CT showed massive destruction of the lung architecture with signs of fibrosis (honeycombing), traction bronchiectasis and superposed diffuse ground glass attenuation. Repeated sputum cultures demonstrated colonisation with *Pseudomonas aeruginosa*. Lung function tests showed a severely decreased vital capacity (25% of the predicted value) and a severely decreased carbon monoxide diffusion capacity (16% of the predicted value). Additional examination, including bronchoscopy with transbronchial biopsies and extensive autoimmune serology (including ANA, extractable nuclear antigen (ENA) and rheumatoid factor), failed to clarify the diagnosis. Tuberculin skin testing was negative, and additional sputum cultures ruled out active tuberculosis.

At that stage, it was concluded that she was suffering from a nonclassifiable fibrotic ILD with severe restriction and hypoxaemia. In view of the fact that the patient deteriorated during admission, she was treated with high-dose prednisone (60 mg daily), after which her clinical condition improved, and she could be dismissed from the hospital.

Two years after the initial presentation, the patient developed signs of sclerodactylia and telangiectasias. Serology was still negative for (anti-Scl-70 or anticentromere) autoantibodies. She was clinically diagnosed as suffering from limited scleroderma, with a fibrosing ILD as its first manifestation. She was turned down for lung transplantation. Ultimately, she died due to recurrent infections with multiresistant *P. aeruginosa*.

DISCUSSION

In this report we describe three patients with systemic sclerosis presenting with a progressive fibrosing interstitial lung disease as the first and only manifestation of disease. In the first patient the presence of anti-Scl-70 autoantibodies suggested systemic sclerosis to be the underlying cause of disease. In the two other subjects, however, anti-Scl-70 antibodies were negative. In these two patients the lung disease preceded other manifestations of systemic sclerosis by several years.

During the course of systemic sclerosis, pulmonary involvement can be observed in most patients. In fact, based upon autopsy studies, ILD can be demonstrated in virtually all patients, and it is observed in both limited and diffuse systemic sclerosis.^{9,10,18-20} Moreover, pulmonary disease is the leading cause of death in patients with systemic sclerosis.¹⁹⁻²² Early recognition of ILD is mandatory since symptoms will occur relatively late in the course of the disease. At that stage the patients may suffer from already severely impaired lung function due to irreversible interstitial fibrosis.

Establishing the diagnosis of ILD in patients with documented systemic sclerosis depends on several diagnostic tests. HR-CT is a widely accepted diagnostic tool to detect interstitial lung disease, and has been proven to be highly superior to the chest X-ray.^{17,23,24} Lung function tests, in particular the diffusion capacity for carbon monoxide, are simple and sensitive tests that may suggest the presence of pulmonary involvement. These tests can be performed routinely during the follow-up of patients.²⁵⁻²⁷ In addition, these tests can be used to monitor the effect of medical intervention. However, although a normal pulmonary function practically rules out the presence of ILD, an abnormal lung function has relatively low specificity since multiple factors can be involved in systemic sclerosis.

In a patient presenting with ILD, the presence of Raynaud's phenomenon²⁸ or positive autoantibodies, such as anti-Scl-70, anti-Jo-1 or rheumatoid factor (RF), may suggest a CVD to be the underlying cause of disease. However, the sensitivity of autoantibodies is low. Only 20 to 30% of patients with systemic sclerosis have anti-Scl-70 antibodies,¹⁰ and even in proven systemic sclerosis with ILD, anti-Scl-70 is absent in ~50% of cases. ACA are reported to be present in 20 to 60% of patients with systemic sclerosis.²⁹ The presence of ACA in these patients is associated with a reduced frequency of ILD.³⁰ These patients, however, have an increased risk of developing pulmonary arterial hypertension.^{10,31} On the other hand, in IIP a positive ANF or RF is present in 10 to 20% of cases without any evidence for a CVD during many years of follow-up.

Histopathologically, two patterns of ILD can be observed in systemic sclerosis. UIP is observed in ~20%, and NSIP in ~80% of patients.^{8,9,18} In contrast to idiopathic UIP

and NSIP, prognosis of systemic sclerosis-associated UIP and NSIP is similar.⁸ Moreover, survival in patients with systemic sclerosis-associated ILD is significantly better than in idiopathic UIP and NSIP.^{18,32}

A number of drugs have been used for the treatment of systemic sclerosis-associated ILD, but none have proven effective.³³ Based upon several retrospective studies only cyclophosphamide appeared promising,^{10,34-38} and was therefore adopted by most physicians, with or without low-dose prednisone, as the therapy of choice to slow down the rate of decline in these patients. The role of corticosteroids is still under debate; however, high-dose corticosteroids, as used in our patients according to idiopathic ILD treatment guidelines, have been reported to be associated with an increased risk for scleroderma renal crisis, and should not be used in these patients.³⁹ Recently, two randomised, placebo-controlled trials with cyclophosphamide were published.^{40,41} One year of oral cyclophosphamide in systemic sclerosis-associated ILD was shown to have a significant but modest beneficial benefit on lung function, and health-related quality of life.⁴⁰ In the second study, 54 patients were randomised to receive low-dose prednisone and six-monthly infusions of cyclophosphamide followed by oral azathioprine or placebo. Although, probably due to lack of power, this trial failed to show a significant difference between treatment and placebo, there was a trend ($p=0.08$) toward statistical significance between the groups in one primary endpoint, i.e. forced vital capacity.⁴¹

CONCLUSION

ILD as the first and only presentation of systemic sclerosis is extremely rare. However, it should be considered in patients with positive ANA and/or Raynaud's phenomenon at presentation. In patients with systemic sclerosis-associated ILD, cyclophosphamide with or without low-dose prednisone should be considered to slow down the rate of decline and to preclude irreversible damage to the pulmonary parenchyma.

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