A 16-year Follow-up Case of Interstitial Pneumonia with Systemic Sclerosis-rheumatoid Arthritis Overlap Syndrome

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Abstract

Interstitial pneumonia is a common and major comorbidity affecting the prognosis of patients with systemic sclerosis (SSc). However, there are few reported cases of SSc-rheumatoid arthritis (RA) overlap-associated interstitial pneumonia. We herein report a case in which the clinical behavior and histopathology of interstitial pneumonia with SSc-RA overlap syndrome was followed over a long clinical course. When clinicians are deciding on the treatment strategy for patients with SSc-RA overlap syndrome-associated interstitial pneumonia, a pathological examination of a surgical lung biopsy may be useful.

Key words: systemic sclerosis, nonspecific interstitial pneumonia, rheumatoid arthritis, overlap syndrome

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Introduction

Systemic sclerosis (SSc) is a connective tissue disorder with an autoimmune background that is characterized by microvascular damage and excessive fibrosis of the skin and internal organs. Pulmonary involvement is common in patients with SSc and most often involves fibrosis or interstitial pneumonia and pulmonary vascular disease leading to pulmonary artery hypertension. Pulmonary manifestations are the leading cause of the disease-related morbidity and mortality in SSc patients (1). However, in some cases of SSc, the disease may overlap with autoimmune diseases, such as rheumatoid arthritis (RA), dermatomyositis/polymyositis, and systemic lupus erythematosus (2). SSc-RA overlap is uncommon, and few cases have been reported (3, 4). To our knowledge, the long-term clinical behavior and histopathology of interstitial pneumonia with SSc-RA overlap syndrome has not been reported previously. We herein report the case of a patient who developed RA five years after being diagnosed with SSc-associated interstitial pneumonia on the basis of lung biopsy findings.

Case Report

The patient, a 61-year-old non-smoking Japanese woman, was admitted to our hospital with a chronic dry cough in June 1999. Fine crackles were heard at the bases of both lungs on inspiration. A computed tomography (CT) scan of the chest showed a reticular shadow and ground-glass opacities at the base of both lungs (Fig. 1). A physical examination revealed Raynaud’s phenomenon, skin thickening on the fingers of both hands, nail fold bleeding, dry eye, and dry mouth. Laboratory examinations revealed the following findings: anti-nuclear antibody (ANA) positivity (×640 with a homogenous and speckled pattern), anti-topoisomerase I (anti-Scl-70) antibody positivity and rheumatoid arthritis particle agglutination (RAPA) (×80). The patient’s serum Krebs von den Lungen (KL)-6 and surfactant protein (SP)-D levels were elevated to 523 U/mL and 309 ng/mL, respec-
We consulted a rheumatologist and subsequently performed skin and lip biopsies. She was diagnosed with diffuse cutaneous SSc and secondary Sjögren syndrome (SjS) based on the biopsy findings.

Respiratory function tests showed evidence of restrictive ventilatory impairment with a forced vital capacity (FVC) of 1.57 L (69.2%, % predicted), a forced expiratory volume in 1 second (FEV1) of 1.41 L, FEV1/FVC ratio of 90.4%, a diffusing capacity of carbon monoxide (DLCO) of 15.4 mL/min/Torr (115.8%, % predicted), and DLCO/alveolar volume ratio of 148% (% predicted). A surgical lung biopsy (SLB) was performed for diagnostic purposes via minithoracotomy from the right S6. The lesion was histologically characterized by dense interstitial fibrosis which was largely maintained in the centriacinar, in the subpleural region and around the vessel. These findings were consistent with nonspecific interstitial pneumonia (NSIP) with a fibrosing pattern.

The partial dilation of the airway was observed from the bronchiole to the alveoli. There was almost no inflammatory cell infiltration around the bronchiole (Fig. 2). Based on the clinical and histological findings, the patient was diagnosed with SSc-associated interstitial pneumonia. She was followed up and treated with an antitussive agent. Additionally, echocardiography was regularly performed, and she underwent right heart catheterization in 2012, which indicated no pulmonary hypertension.

**Discussion**

We herein report a case of SSc-RA overlap syndrome associated with interstitial pneumonia. This is an important report that describes a valuable case with a 16-year follow-up period in which the appropriate therapy was selected based on the pathological findings of an SLB specimen. SSc-associated interstitial pneumonia is currently considered to be the major cause of death (due to respiratory failure or fatal pulmonary hypertension) in SSc. Interstitial lung disease (ILD) occurs in up to 80% of SSc patients, making ILD more prevalent in SSc than in any other connective tissue disease. The major risk factors for the development and progression of lung fibrosis are male gender, the diffuse cutaneous SSc subtype, the presence of anti-Scl-70 antibodies, an FVC of <70%, and the extent of fibrosis at the baseline (5).

The major characteristic histological features of ILD in SSc are dense interstitial fibrosis and pulmonary hypertensive vascular changes. The most common pattern of interstitial pneumonia in SSc is NSIP with a fibrosing pattern, manifesting as dense interstitial fibrosis with scarce inflammatory cells and paucicellular interstitial fibrosis that maintains the underlying lung architecture and often spares the immediate subpleural area (6). The estimated prevalence of RA-associated ILD among RA patients is 19-56% (7, 8), RA-associated ILD is generally associated with male gender, a lower DLCO value, demonstrating a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT), and characteristic histopathological features. The histological features in RA patients can be UIP or NSIP, with UIP being more common (7-9). The occurrence of more prominent interstitial lymphoid aggregates, either within the alveolar septal walls or in the small airways, and inflammatory airway disease (including bronchitis and bronchiolitis) have been noted (6). In addition, inflammatory small airway disease might be a secondary finding in the
Figure 2. Histological images. (A) The lesion was characterized by dense, interstitial fibrosis, which was largely maintained in the centriacinar, the subpleural region, and around the vessel (Hematoxylin and Eosin (H&E) staining, ×25). (B) Partial dilation was observed from the bronchiole to the alveoli. There was almost no inflammatory cell infiltration around the bronchiole (H&E staining, ×100).

Figure 3. The clinical course. In the initial 5-year period of SSc-associated interstitial pneumonia, the patient’s forced vital capacity (FVC) was moderately decreased, and the serum level of KL-6 remained high. After the diagnosis of SSc-RA overlap syndrome, treatment with prednisolone (PSL) (2.5-5 mg/day) and bucillamine was initiated and maintained. This resulted in a very slight increase in the patient’s FVC and the normalization of the serum level of KL-6. The fibrosis in the lung progressed and formed a honeycomb lesion in the lower lung.

background of RA-associated UIP or NSIP (10).

RA sometimes overlaps with other collagen diseases. The prevalence of SSc-RA overlap syndrome is approximately 5% (11). SSc-RA overlap patients have long-term SSc with various internal organ manifestations that are later complicated by the development of RA, usually 1-16 years after the onset of SSc. Erosive polyarthritis (82%), pulmonary fibrosis (77%), esophageal involvement (55%), and cardiac manifestations (50%) are most commonly observed in SSc-RA overlap patients (11). The findings of high anti-CCP antibody titers may help to define the diagnosis of SSc-RA overlap syndrome and facilitate the diagnosis and appropriate treatment: the serum anti-CCP antibody titer is higher in patients with SSc-RA overlap syndrome than in SSc patients with/without arthralgia (12, 13). In the present case, SSc-RA overlap syndrome was diagnosed based on the presence of several compatible features.

However, the clinical behavior and histopathology of interstitial pneumonia with SSc-RA overlap syndrome has not been reported previously. Regarding the clinical behavior, SSc-ILD progresses much more frequently in the first four years of systemic disease (especially in the first two
years) (14). In our case, in the initial five-year period of SSc-associated interstitial pneumonia, the patient’s FVC moderately decreased, while the serum level of KL-6 remained high. Thereafter, although the fibrosis in the patient’s lung progressed to form a honeycomb lesion, the decrease in the patient’s FVC was very slight, and the serum level of KL-6 normalized. This clinical behavior was similar to that of SSc-NSIP. Furthermore, the histopathological findings in our patient’s lung specimens showed dense interstitial fibrosis with scarce inflammatory cells that maintained the underlying architecture and often coexisted in an interwoven normal lung area. These findings were compatible with the typical characteristics of SSc-NSIP. The interstitial lymphoid aggregates and inflammatory airway lesions that are often seen in patients with RA-ILD were not observed in our patient. However, the pathological findings may change after the development of SSc-RA, as the radiological findings initially showed new consolidations and thickened reticulation (in 2004), subsequently shifting to definite honeycomb with thinner walls (in 2010) after the development of RA. We therefore observed radiological changes, with the area of fibrosis becoming confluent and beginning to appear as a honeycomb lesion. These radiological changes are seen often, even in cases of NSIP with SSc-ILD (6). However, not only SSc, but also RA, might affect the occurrence of pathological pulmonary changes at this point, due to the fact that there is a possibility of radiological honeycomb lesions forming as a result of RA itself.

Regarding the treatment of ILD, the optimum treatment of RA-ILD and SSc-ILD remains to be established. RA-ILD is treated empirically and typically includes corticosteroids and/or immunomodulating/steroid-sparing agents. However, given the lack of convincing benefit with this therapy and the increased risk of SSc renal crisis, the indication for moderate- to high-dose corticosteroid therapy SSc-ILD is limited. Furthermore, there has been no consensus about the indications for SLB in cases of connective tissue disease-ILD, such as RA and SSc (15). In our case, the SLB specimen revealed the scarcity of inflammatory cells in pathological NSIP with a fibrosing pattern. Therefore, we were able to avoid needless corticosteroid therapy, and a pathological examination of the SLB specimen was thought to be useful for devising a treatment strategy for ILD. However, in our case, as far as the FVC and serum KL-6 level were concerned, low-dose corticosteroid therapy seemed to stabilize the progression of the disease from 2004. The accumulation of further cases is needed in order to determine whether or not this therapy is effective for SSc-ILD.

In conclusion, we herein described a case of SSc-RA overlap syndrome-associated interstitial pneumonia. Because this syndrome sometimes occurs, it is clinically important to check for the occurrence of RA in patients with established SSc. When determining the treatment strategy for patients with SSc-RA overlap syndrome-associated interstitial pneumonia, the pathological findings of the SLB specimen may be useful.

The authors state that they have no Conflict of Interest (COI).

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