

Sarcoidosis in a Patient with Systemic Sclerosis and Primary Biliary Cirrhosis

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Abstract

A 73-year-old woman who had been diagnosed with systemic sclerosis was admitted for further examination of bilateral hilar lymphadenopathy. Sarcoidosis was confirmed based on elevated serum levels of angiotensin-converting enzyme, a high proportion of lymphocytes and a high CD4/CD8 ratio in bronchoalveolar lavage fluid, abnormal ⁶⁷Gallium uptake in the mediastinum and noncaseating granulomas in skin biopsy specimens. In addition, high levels of antimitochondrial M2 antibodies and alkaline phosphatase indicated primary biliary cirrhosis (PBC). Here we describe a rare triplex of sarcoidosis, SSc and PBC. Although the etiology of this complex remains unknown, these three diseases might share some pathogenesis.

Key words: sarcoidosis, systemic sclerosis, primary biliary cirrhosis, CREST syndrome

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Introduction

Sarcoidosis is a granulomatous disorder of unknown etiology that characteristically involves several organs. Although sarcoidosis does not meet the criteria for autoimmune disease, it can coexist with a wide range of autoimmune disorders. Sarcoidosis has been described in association with Sjögren's syndrome, polymyositis, systemic lupus erythematosus, ankylosing spondylitis, inclusion body myositis, remitting seronegative syndrome, and systemic sclerosis (SSc) (1, 2). Since autoantibodies, circulating immune complexes, and altered lymphocyte function are common to these diseases, they may all be part of a predisposition to autoimmune disease (3). Here, we describe a rare case of sarcoidosis coexistent with SSc and primary biliary cirrhosis (PBC).

Case Report

A 73-year-old woman was admitted to our hospital for further examination of bilateral hilar lymphadenopathy. She had been diagnosed 6 months previously with systemic scler-

osis based on swollen fingers, pigmentation at the dorsal surface of the fingers, Raynaud's phenomenon and elevated levels of anticentromere antibody.

A physical examination upon admission revealed body temperature, 36.7°C, blood pressure, 112/72 mmHg and a regular pulse of 72 beats/min. No superficial lymphadenopathy was evident. Lung and heart auscultation was normal. Abdominal examination revealed no hepatomegaly. Skin examinations revealed swollen fingers, pigmentation at the dorsal surface of both hands and fingers, blood spots at the nails and precordial telangiectasis. The extracutaneous features of SSc including esophageal dysmotility, renal insufficiency and pulmonary hypertension were not seen.

Laboratory tests upon admission revealed that the patient was positive for serum anti-nuclear antibody (ANA; ×640, anticentromere) and serum levels of anticentromere antibody were elevated (186.1, reference range: <16). Serum levels of IgM (134 mg/dL) and total cholesterol (208 mg/dL) were normal. Rheumatoid factor, as well as anti-SS-A, anti-SS-B, anti-Sm, anti-Scl-70, and anti-DNA antibodies were all negative. Serum levels of γ -globulin (1.6 g/dL) and angiotensin-converting enzyme (ACE; 42.4 U/L) were elevated. Serum and urine levels of calcium were normal. Anti-

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Figure 1. Chest X-ray showed bilateral hilar lymphadenopathy.

human T-lymphotrophic virus type 1 was positive. Chest X-rays (Fig. 1) and computed tomography (CT) images showed mediastinal and bilateral hilar lymphadenopathy. The total cell count ($3.4 \times 10^5/\text{mL}$) in bronchoalveolar lavage fluid was increased with a high proportion of lymphocytes (90.5%) and a high CD4/CD8 ratio (4.0). Transbronchial lung biopsy (TBLB) specimens were free of abnormalities such as alveolitis or granulomas. The tuberculin skin reaction was positive. Scintigraphy revealed abnormal ^{67}Ga uptake by the mediastinum. Skin biopsy specimens obtained from the dorsal surface of the right hand revealed noncaseating granulomas (Fig. 2). The above findings indicated a diagnosis of sarcoidosis. In addition, the level of antimitochondrial M2 antibodies that comprise a specific marker of primary biliary cirrhosis was remarkably elevated (147.7, reference range: <7) with elevated alkaline phosphatase levels. Abdominal CT revealed no abnormal findings. The patient refused to undergo a liver biopsy. However, these findings indicated a diagnosis of sarcoidosis and primary biliary cirrhosis accompanied by SSc. The oral administration of ursodeoxycholic acid stabilized the liver dysfunction.

Discussion

Here we described a patient with coexisting sarcoidosis, SSc and PBC, each of which is associated with other autoimmune diseases (1, 2, 4, 5). The co-existence of PBC and SSc is recognized (6). Both are both chronic, presumed autoimmune conditions usually affecting middle-aged females. One report indicates that 84% of patients with PBC also have one other autoimmune disease, while 40% have two or more (4). The prevalence of SSc (most of which is cutaneous) in patients with PBC is 3-8% (4, 7, 8). Conversely, the estimated prevalence of PBC among patients with SSc is 2.5-3% (4) and 25% of patients with SSc are positive for antimitochondrial antibodies, which comprise a

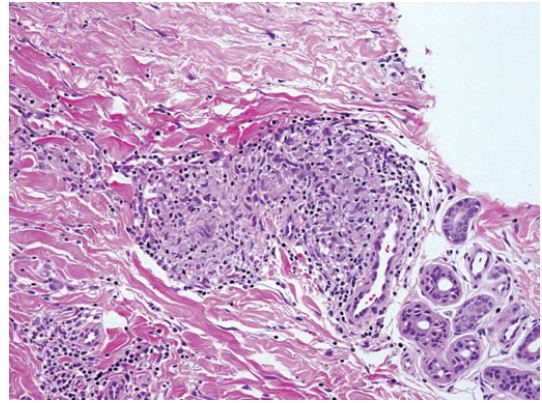


Figure 2. Skin biopsy specimens from the dorsal surface of the right hand. Hematoxylin and Eosin staining revealed non-caseating granulomas ($\times 40$).

specific marker of PBC (9, 10). Liver disease progresses more slowly in PBC-SSc compared with matched patients who have only PBC (7). Although the autoimmune mechanisms behind the PBC-SSc association are not fully understood, Mayo et al reported that antigen-stimulated T cells might play an important role in both diseases (11). They demonstrated that overexpression of TCRBV3, a T-cell receptor beta chain variable region, is related to stable clonal expansion within the CD8(+) T-cell population and associated with clinical expression of the CREST syndrome, a limited variant of progressive systemic sclerosis, in patients with PBC (11). Meanwhile, T-cell receptor gene expression differs among patients, with one distinct exception: the T cells expressing TCRAV2S3 that circulate in patients with sarcoidosis who are positive for HLA-DRB1*0301 (12).

Some case reports have described coexisting sarcoidosis and SSc, but the association between them is not fully understood, although genetic factors similar to those associated with sarcoidosis appear to influence the clinical course of the disease. The incidence of SSc is higher among African-Americans than among Nigerian blacks (2).

Kishor et al recently reviewed 17 patients with sarcoidosis and PBC and suggested that a common pathway contributes to granuloma formation in both disorders (13). One explanation for the apparent association between these conditions is that both share a similar defect in cell-mediated immunity. On the other hand, no significant association has been identified in a large database in the United Kingdom (14), and an ACE gene insertion/deletion polymorphism has been linked to sarcoidosis, which does not affect the susceptibility to or prognosis of PBC (15).

In conclusion, we described a patient with a triplex of sarcoidosis, SSc and PBC. Although the etiology of this complex remains unknown, these three diseases might share a similar pathogenesis.

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