Sarcoidosis Associated with Connective Tissue Diseases: Report of 3 Cases

Shinichi Ishioka, Yuji Yamanishi, Keiko Hiyama, Akihiro Maeda, Hiroyuki Maeda and Michio Yamakido

Disease activity in Japanese sarcoidosis patients is generally mild. However, the pulmonary sarcoidosis coexisting with connective tissue disease is likely to be progressive. We report here three cases of sarcoidosis coexisting with connective tissue diseases, who developed pulmonary manifestations from stage II to stage III. (Internal Medicine 38: 984-987, 1999)

Key words: rheumatoid arthritis, systemic sclerosis, Sjögren’s syndrome, disease activity

Introduction

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. Abnormal immune function, such as positive rheumatoid factor (RF) and antinuclear antibodies (ANA), and pulmonary involvement that may progress from alveolitis to pulmonary fibrosis are frequently observed in sarcoidosis, as well as in connective tissue diseases. Therefore, similar immunopathogenic mechanisms have been considered in both conditions, but there are relatively few reports of sarcoidosis patients associated with connective tissue diseases (1–3).

We describe three patients with sarcoidosis and coexistent connective tissue diseases, including rheumatoid arthritis, Sjögren’s syndrome, and systemic sclerosis.

Case Report

Case 1

A 73-year-old woman with sarcoidosis was admitted to our hospital due to a 4-month history of bilateral knee and wrist arthralgia. Six years before admission, she was diagnosed as having sarcoidosis by the presence of bilateral hilar lymphadenopathy (BHL) and multiple small nodular shadows in chest X-ray (sarcoidosis Stage II), high serum level of angiotensin-converting enzyme (s-ACE), and typical histological findings of a transbronchial lung biopsy specimen. Rheumatoid factor and antinuclear antibody were negative, and she had no joint symptoms at that time.

Physical examination revealed joint swelling and pain of the metacarpophalangeal (MCP), proximal interphalangeal (PIP), and wrist joints of both hands. Blood examination showed an elevated erythrocyte sedimentation rate (ESR) 80 mm/h and C-reactive protein (CRP) 2.9 mg/dl, and positive RF 452.5 IU/l (normal <6 IU/l), which had changed from negative 2 months before admission, and positive ANA (1:320, speckled). The hand X-ray showed erosive change between the trapezium and first metacarpal joints and the chest X-ray showed reticulonodular shadows and honeycombing in the middle to lower fields (Stage III, Fig. 1). The patient was diagnosed as having RA according to the 1987 American College of Rheumatology (ACR; formerly, the American Rheumatism Association) revised criteria for RA (4), and methotrexate therapy (MTX), in addition to small doses of prednisolone (5 mg/day) and nonsteroidal anti-inflammatory drugs (NSAIDs), was started. Two months after administration of MTX, the patient’s joint symptoms had almost disappeared, associated with a decrease in the CRP level to 0.7 mg/dl.

Case 2

A 48-year-old woman with systemic sclerosis was admitted to our hospital complaining of dyspnea and died of respiratory failure one month later. When she was 29 years old, she was diagnosed as having generalized systemic sclerosis by the presence of Raynaud’s phenomenon, proximal scleroderma skin changes, sclerodactyly, desquamative skin change, and pulmonary fibrosis. Although chest X-rays showed BHL and small nodular shadows (sarcoidosis Stage II, Fig. 2A), she was not diagnosed as having sarcoidosis at that time. Four years later, the biopsy specimen of the right supraclavicular lymph node revealed noncaseating granuloma consistent with sarcoidosis, and thus sarcoidosis was histopathologically diagnosed. Serological examination showed positive ANA (1:160, speckled) with negative anti-RNP antibodies. When she was 45 years old, exertional dyspnea increased and chest X-ray showed diffuse

From the Second Department of Internal Medicine, Hiroshima University School of Medicine, Hiroshima
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Reprint requests should be addressed to Dr. Shinichi Ishioka, the Second Department of Internal Medicine, Hiroshima University School of Medicine, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551

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interstitial fibrotic changes with restrictive pulmonary dysfunction (Stage III, Fig. 2B). Three years later, the pulmonary fibrosis had progressed (Fig. 2C), and the patient died of respiratory failure.

**Case 3**

A 58-year-old woman with a 7-month history of keratoconjunctivitis sicca (KCS) and xerostomia was admitted to our hospital for evaluation of increasing dyspnea on exertion. Chest roentgenogram showed BHL and reticular nodular shadows in both upper and middle lung fields (Stage II, Fig. 3A). Blood examination revealed elevated levels of liver-associated enzyme and s-ACE. Transbronchial lung biopsy and liver biopsy specimens showed noncaseating granulomas consistent with sarcoidosis. KCS was confirmed from a positive Shirmer’s test and Rose-Bengal test. Biopsy of the minor salivary gland showed moderate lymphocytic infiltration without granuloma, consistent with Sjögren’s syndrome. This patient was diagnosed as having sarcoidosis with lung and liver involvement and coexisting Sjögren’s syndrome, therefore, high dose corticosteroids (PSL 60 mg/day) were administered. During therapy, osteoporotic change and lumbar fractures, which were considered as side effects of corticosteroids, were observed. Cyclophosphamide was added with a gradual lowering of corticosteroids and liver function steadily improved. However, the fibrotic changes in chest X-ray progressed and the chest roentgenogram two years later showed reticulonodular shadows (Stage III, Fig. 3B).
Discussion

Similarities between connective tissue diseases and sarcoidosis have been recognized since 1946 (5) and several authors have suggested shared immunopathogenic mechanisms (1, 2, 6). Sarcoidosis is considered to be an antigen-driven, Th1-mediated granulomatous disorder, dominated by expression of IFNγ and IL12, and if the Th1 response is not downregulated, active TGFβ could serve to promote fibrosis given its potent profibrotic effect (7). Autoimmune diseases are also considered to be dependent on Th1 or Th2 cells: rheumatoid arthritis is an example of a Th1 dominant disorder and SLE shows a shift toward Th2 (8). Although reports of coexisting sarcoidosis and connective tissue diseases are rare, sarcoidosis has been reported to be complicated with several types of connective tissue diseases including rheumatoid arthritis (9), systemic sclerosis (10), Sjögren’s syndrome (11), and systemic lupus erythematosus (SLE) (12). We described three cases (4%) of sarcoidosis complicated by rheumatoid arthritis (case 1), systemic sclerosis (case 2), or Sjögren’s syndrome (case 3), from among 73 sarcoidosis cases who were admitted to our department over a 10-year period. All three were middle aged to elderly women (Table 1). In case 1, rheumatoid arthritis was diagnosed six years after the onset of sarcoidosis. In case 2, systemic sclerosis was diagnosed four years before the diagnosis of sarcoidosis although the chest X-ray showed BHL at that time. In case 3, Sjögren syndrome and sarcoidosis were diagnosed simultaneously. In the reported association of rheumatoid arthritis and sarcoidosis, no patient with sarcoidosis subsequently developed rheumatoid arthritis, and case 1 was the first such case. Kucera (9) reported two cases with sarcoidosis in Stage I and Stage III which developed in patients with rheumatoid arthritis. Others (2, 13) have reported Stage I, II, and III cases, indicating any stage may be observed. Interestingly, when case 1 was diagnosed as RA, BHL was disappearing and fibrotic change in the interstitium was progressing; this indicated it was developing from Stage II to Stage III. In a majority of the reported cases with coexistent systemic sclerosis and sarcoidosis (10, 14), sarcoidosis was diagnosed several years after the onset of systemic sclerosis, as in the present case 2. It is reported that sarcoidosis associated scleroderma appeared to be severe and persistent, and the possibility of a common cause of sarcoidosis and scleroderma, in particular, the role of exposure to silica was suggested (14). In case 2, no common cause of systemic scleroderma and sarcoidosis was found, but

Table 1. Clinical Course of Patients with Sarcoidosis and Connective Tissue Diseases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Disease**</th>
<th>Stage*** (ACE: U/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67† → 73†</td>
<td>rheumatoid arthritis</td>
<td>II (27.2)* → III (19.0)</td>
</tr>
<tr>
<td>2</td>
<td>29† → 33† → 48</td>
<td>systemic sclerosis</td>
<td>II (35.0)* → III (7.8)</td>
</tr>
<tr>
<td>3</td>
<td>58† → 60</td>
<td>Sjögren’s syndrome</td>
<td>II (41.7)* → III (23.1)</td>
</tr>
</tbody>
</table>

* at diagnosis of sarcoidosis, † at diagnosis of connective tissue diseases, **Connective tissue diseases associated with sarcoidosis, ***Chest X-ray stage of sarcoidosis.
the clinical symptoms were severe. Although the diagnosis of sarcoidosis was confirmed four years after the diagnosis of systemic scleroderma, BHL and paratracheal lymph node swelling with pulmonary fibrosis were found when the diagnosis of systemic sclerosis was first carried out. At that time, these findings were considered as lung involvement of progressive systemic sclerosis. After the diagnosis of sarcoidosis, the lymph node swelling disappeared and the fibrotic change in the lung field progressed and finally the patient died of respiratory failure. As a pulmonary manifestation in systemic sclerosis, BHL or paratracheal lymph node swelling are rare. Thus, if they are observed, coexistence of sarcoidosis should be considered.

Since both sarcoidosis and Sjögren syndrome cause glandular involvement and sicca features, biopsy of labial minor salivary glands is a highly discriminatory method of distinguishing between sarcoidosis and Sjögren’s syndrome. Case 3 was primary Sjögren syndrome accompanying severe liver sarcoidosis and progressive pulmonary sarcoidosis. It is reported that the chest roentgenogram showed BHL in 45% of coexisting cases with Sjögren syndrome and sarcoidosis, interstitial pneumonia in 27%, and no abnormality in 36% (2, 15). In the present case, although the liver function was improving due to treatment with corticosteroids and cyclophosphamide, the pulmonary lesion was progressing slowly. With regard to the severity and activity of sarcoidosis, case 1 was mild, but the pulmonary lesion was progressive. In case 2, although the evaluation of the cause of the severe pulmonary fibrosis was difficult, it might be considered that coexistent systemic sclerosis and active sarcoidosis induced severe pulmonary fibrosis. In case 3, liver sarcoidosis was clinically severe and active, and pulmonary lesions were progressive even under the treatment of corticosteroids and immunosuppressants. In all three cases, pulmonary sarcoidosis was progressive and case 2 died of pulmonary fibrosis. It is distinctive compared with reported general prognosis for sarcoidosis: only 14% (16) (p=0.00343, Fisher’s exact test) or 19.3% (17) (p=0.00947, Fisher’s exact test) of Stage II patients progressed to Stage III. Of course, we could not exclude the possibility that the progressing pulmonary lesions were due to the associated connective tissue diseases in these patients, since pathological re-evaluation of interstitial infiltrates is uncommon in patients with definite diagnosis of sarcoidosis. However, considering the hypothesis that evolution of Th1 immune response into Th2 response could be associated with an increased risk of developing fibrocytic changes in sarcoidosis (7) and autoimmune diseases are dependent on a delicate balance between Th1 and Th2 cells (8), association of connective tissue diseases in sarcoidosis patients could be the juncture of developing fibrosis.

In general, disease activity in Japanese sarcoidosis cases is mild and almost all pulmonary lesions will regress spontaneously. However, the sarcoidosis coexisting with connective tissue disease showed high activity and especially the pulmonary lesions were progressive from the BHL stage to the fibrotic stage. Progressive pulmonary sarcoidosis would suggest possibly coexisting connective tissue diseases.

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References