Association of Progressive Systemic Sclerosis with Pulmonary Sarcoidosis. Just a Chance Occurrence?

Toru Takahashi, Mitsuru Munakata, Yukihiko Homma* and Yoshikazu Kawakami

A 46-year-old Japanese woman has been followed up for 3 years due to interstitial pneumonia associated with progressive systemic sclerosis (PSS). During this follow-up period, chest roentgenogram revealed additional diffuse nodular shadows. She was diagnosed as having pulmonary sarcoidosis, which was confirmed by the presence of epitheloid granulomas within the alveolar septa. She was successfully treated with corticosteroids and recovered almost completely without worsening pulmonary abnormalities caused by her PSS. The independent clinical courses of these two diseases in the present case suggest that the complication of PSS and sarcoidosis in this patient may be coincidental.

Key words: autoimmune disorder, interstitial pneumonia, bronchoalveolar lavage, granuloma, corticosteroids

Introduction

Sarcoidosis has been reported to show immunological abnormalities related to cellular immune abnormalities such as T-helper lymphocytic dys- and/or hypo-function similar to autoimmune diseases (1, 2). Not only progressive systemic sclerosis (PSS), but also Hashimoto’s thyroiditis, idiopathic thrombocytopenia, rheumatoid arthritis, and other autoimmune disorders are reported to exist with sarcoidosis (3–9). Here, we describe a patient with interstitial pneumonia associated with PSS. This was complicated with sarcoidosis 3 years after the diagnosis of PSS and treated successfully with corticosteroids without modifying the underlying abnormalities associated with PSS, including interstitial pneumonia. Although previous case reports concerning the coexistence of PSS and sarcoidosis have discussed similar immunoreactions of the two diseases, the present case showed the possibility that these two diseases could have a different pathogenesis.

Case Report

A 46-year-old woman was admitted to Hokkaido University Hospital in 1989 because of Raynaud’s phenomenon, trophic finger changes, scars on fingertips, shoulder stiffness, and dysphagia. She was diagnosed as having PSS because of histological proof of skin lesions, and as having interstitial pneumonia in association with PSS (PSS-IP) because of infiltrative shadows and honeycomb formation in bilateral lower lung fields in chest roentgenograms and computed tomography (CT) scans, as well as histological alveolitis in transbronchial lung biopsy (TBLB). In November 1992, her occasional chest roentgenogram revealed bilateral diffuse infiltrative shadows with no respiratory symptoms and she was re-admitted for further investigation. She had smoked 10 cigarettes daily for 20 years. Chest auscultation revealed inspiratory fine crackles over the lower lungs bilaterally. Her fingers were red and edematous, but she developed no eczema or nodules. The chest roentgenogram on re-admission showed diffuse small nodular opacities in the whole lungs, especially in the upper and middle lung fields, and infiltrative shadows in bilateral lower lung fields. In a chest CT scan (Fig. 1, top), diffuse ground glass opacities and small nodular opacities were recognized. Electrocardiogram findings showed multi-focal premature ventricular contractions, which were recorded four times per day, but an ultrasonic cardiograph and thallium myocardial scan were within normal ranges. A gallium-67 lung scan revealed diffuse uptake except for bilateral lower lungs. She had a negative tuberculin test (2×2 mm). Routine laboratory data on admission revealed an increased erythrocyte sedimentation rate (70 mm/h) and decreased lymphocytes (6%), but normal hepatic and renal functions. Serological examination showed hypergammaglobulinemia (29.2%), high serum immunoglobulin A and G (247 mg/dl and

From the First Department of Medicine and *Medical Administration Center, School of Medicine, Hokkaido University, Sapporo
Received for publication November 11, 1996; Accepted for publication March 13, 1997
Reprint requests should be addressed to Dr. Toru Takahashi, the First Department of Medicine, School of Medicine, Hokkaido University, N-15, W-7, Kita-ku, Sapporo 060

Internal Medicine Vol. 36, No. 6 (June 1997)
Takahashi et al

Figure 1. Chest CT scan on second admission (1993/11/25) shows diffuse ground glass and small nodular opacities throughout upper lung fields, and infiltrative shadows in middle and lower lung fields. Infiltrative shadows and micro honeycomb lung located in lower lung fields (top). Chest CT scan after corticosteroid treatment (1994/2/10) shows almost completely healed shadows and the remaining honeycomb lung (bottom).

2,963 mg/dl, respectively), and low immunoglobulin E (IgE) (2 IU/l) levels. The serum angiotensin-converting enzyme (ACE) level was normal (14.6 mg/dl), but it was higher than the level at the first admission (8.6 mg/dl), and the genotype was II, which is common in Japanese and is associated with low serum ACE levels. As for autoimmune antibodies, anti-nuclear antibody gave a diffuse, homogeneous, and speckled staining pattern and anti-SS-A antibody was also positive, but anti-DNA, anti-SS-B, and anti-Scl-70 antibodies were all negative. Pulmonary functions revealed worsening of restrictive ventilatory abnormalities and carbon monoxide diffusing capacity as shown in Table 1. Arterial blood gas analysis during room air breathing showed: pH 7.418; P02 78 mmHg; Pco2 45.4 mmHg.

TBLB was performed at the right upper and basal segments (S3 and S8) and microscopic examination (Fig. 2) showed epitheloid granulomas of several sizes within the alveolar septa and alveolar cavities. No foreign body depositions, necrosis, or caseations could be recognized. These pathological findings were different from specimens obtained in the first admission in the thickness of the alveolar septum with mononuclear cell infiltration and the destruction of normal alveolar structure.

No abnormalities were recognized in ocular examinations and there were no other abnormalities, except for PSS, including histological abnormalities in dermal examinations. The liver biopsy specimen revealed no granulomas. A myocardial biopsy was not performed. Bronchoalveolar lavage (BAL) was performed from left S4, which was normal, and right S2, which reflected the abnormal opacities. There was an increase in total cell counts, lymphocyte ratio and CD4/CD8 in BAL fluid (BALF) and these findings were consistent with pulmonary sarcoidosis (Table 1). Her clinical course for respiratory functions and BALF findings is shown in Table 1.

We diagnosed that the additional pulmonary abnormal shadows were due to pulmonary sarcoidosis. We treated her with corticosteroids (0.5 mg/kg tapered off in 12 months), and after this treatment, her additional pulmonary opacities were completely resolved (Fig. 1, bottom). There were also improvements of pulmonary functions and BALF findings (Table 1). However, her basilar interstitial pneumonia and systemic feature of PSS remained unchanged throughout this period.

Discussion

The association of autoimmune disorders and sarcoidosis has been repeatedly reported. In 1946, Teilum (10) reported similarities between connective tissue disease and granulomatous disease, and after this report, several reports proposed relationships between these two diseases. In 1974, Bara et al (11) first reported a case of sarcoidosis coexisting with PSS, and Wiesenhutter and Sharma (12) reported three cases with PSS and one case with SLE, with a review of the literature, and Maekawa and Nogami (9) reported one case of PSS and sarcoidosis with esophageal adenocarcinoma. Some case reports have discussed sarcoidosis coexisting with autoimmune diseases such as Hashimoto’s thyroiditis, idiopathic thrombocytopenia, and rheumatoid arthritis (3–8). However, the coexistence of sarcoidosis and connective diseases seems to be rare. James and Williams (1) and Needleman et al (2) thought that both sarcoidosis and autoimmune disorders have similar

436 Internal Medicine Vol. 36, No. 6 (June 1997)
**PSS-IP and Pulmonary Sarcoidosis**

### Table 1. Clinical Course of Respiratory Function and BALF Findings

<table>
<thead>
<tr>
<th></th>
<th>1989/5/10 (1st Admission)</th>
<th>1992/12/10 (2nd Admission) before CS Tx</th>
<th>1993/2/7 (2nd Admission) during CS Tx</th>
<th>1994/3/1 after 12 months of CS Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary Functions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VC (L)</td>
<td>1.57 (60*)</td>
<td>1.37 (53*)</td>
<td>1.27 (49*)</td>
<td>1.43 (56*)</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>1.33 (59*)</td>
<td>1.22 (55*)</td>
<td>1.23 (55*)</td>
<td>1.25 (58*)</td>
</tr>
<tr>
<td>TLC (L)</td>
<td>2.74 (73*)</td>
<td>2.22 (59*)</td>
<td>2.53 (67*)</td>
<td>2.75 (73*)</td>
</tr>
<tr>
<td>FRC (L)</td>
<td>1.90 (84*)</td>
<td>1.46 (64*)</td>
<td>2.28 (72*)</td>
<td>1.87 (81*)</td>
</tr>
<tr>
<td>RV (L)</td>
<td>1.15 (94*)</td>
<td>0.85 (68*)</td>
<td>1.10 (88*)</td>
<td>1.38 (108*)</td>
</tr>
<tr>
<td>DLco (ml/min/mmHg)</td>
<td>14.60 (91*)</td>
<td>8.93 (59*)</td>
<td>10.42 (68*)</td>
<td>9.52 (61*)</td>
</tr>
<tr>
<td>DL/VA (ml/min/mmHg/l)</td>
<td>5.39 (81*)</td>
<td>4.68 (92*)</td>
<td>4.82 (95*)</td>
<td>4.58 (90*)</td>
</tr>
<tr>
<td>BALF findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cells (x10^3/ml BALF)</td>
<td>16.5</td>
<td>34.4</td>
<td>16.8</td>
<td>12.8</td>
</tr>
<tr>
<td>Cell differentiation (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>macrophage</td>
<td>80.0</td>
<td>36.7</td>
<td>68.4</td>
<td>92.8</td>
</tr>
<tr>
<td>lymphocyte</td>
<td>19.4</td>
<td>61.4</td>
<td>31.2</td>
<td>6.2</td>
</tr>
<tr>
<td>neutrophil</td>
<td>0.2</td>
<td>0.6</td>
<td>0.2</td>
<td>0.8</td>
</tr>
<tr>
<td>eosinophil</td>
<td>0.2</td>
<td>1.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>others</td>
<td>0.2</td>
<td>0.4</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>CD4/8</td>
<td>1.11</td>
<td>6.73</td>
<td>2.25</td>
<td>1.61</td>
</tr>
</tbody>
</table>


Figure 2. Transbronchial lung biopsy specimen from right S3 and S8 consisted of several sizes of epitheloid granulomas within the alveolar septa and alveolar cavities (HE stain, original magnification, ×200).

Immunoregulatory defects such as T-helper lymphocytic dysfunction/hypo-function, and Yagura et al (13) explained immunological similarities between sarcoidosis and collagen vascular diseases such as the same cytokine activities, which may lead to decreased serum IgE levels. Furthermore, Wiesenhutter and Sharma (12) explained that sarcoidosis is similar to PSS or SLE in the profile of humoral and cellular immune abnormalities such as decreased T lymphocytes or activated B lymphocytes. Both PSS and sarcoidosis have decreased lymphocyte reactivity to mitogens in vitro (14–16). There are also decreases in the numbers of peripheral lymphocytes and T-cells in both PSS and sarcoidosis. The decreased T-cells are mainly suppressor (CD8) T lymphocytes and CD4 lymphocyte alveolitis has been observed in sarcoidosis. On the other hand, helper (CD4) T lymphocyte and CD8 lymphocyte alveolitis is observed in PSS (17–19). These facts suggest that it is not easy to find a unified explanation for the pathogenesis of sarcoidosis and PSS.

This case was diagnosed as PSS and PSS-IP by means of the histological findings of dermal and lung biopsies, followed by sarcoidosis diagnosed through serological examinations and lung biopsy. Sarcoidosis improved on corticosteroid treatment, but PSS and PSS-IP remained unchanged in chest CT scans.

The possibility of coexistence of these two diseases should
be discussed. The exact prevalence of PSS is unknown, but in
Japanese is estimated to be 5.05 cases per 100,000 population
when calculated from the data of Takehara et al (20). The
prevalence of sarcoidosis in Japanese is estimated to be 5.34
cases per 100,000 population by Hiraga (21). Though the
coexistence of these two diseases is considered to be very rare
judging from the above data, at least seven cases have been
reported. These results suggest the existence of a relationship
between PSS and sarcoidosis.

Two questions arose in the present case. The first was
whether the lung involvement and dermal involvement diag-
nosed at first admission might have been due to sarcoidosis. The
second was whether the exacerbated pulmonary shadows diag-
nosed as pulmonary sarcoidosis could have been due to the
exacerbation of PSS-IP. Dermal findings on first admission
showed Raynaud’s phenomenon, trophic fingers, scars on
fingertips, and shoulder stiffness, and microscopic findings
showed inner skin fibrosis and micro-capillaritis, findings that
were in accord with PSS, not sarcoidosis. Pulmonary involve-
ment on first admission showed infiltrative shadows and honey-
comb formation in bilateral lower lung fields on chest CT scans
and pathological findings revealed cell infiltration and thick-
ened interstitium without any granulation, suggesting intersti-
tial pneumonia. That diagnosis was supported by restrictive
impairment in lung function tests and a gallium-67 lung scan
showing no uptake in bilateral lower lungs. Furthermore, as the
chest CT scan on second admission showed diffuse ground
glass opacities and small nodular opacities throughout the
upper lung fields and biopsied specimens showed various sizes
of epithelioid granulomas within the alveolar septa and alveolar
cavities, these findings were in accord with sarcoidosis. El-
evated serum ACE levels and decreased IgE levels, BALF
findings from right S2 of increased total cell counts, lymphocyte
ratio and CD4/8 ratio, as well as decreased total lung capacity
and permeability suggested the possibility of active sarcoi-
dosis. It is true that sarcoidosis shows interstitial pneumonia in its
end stage, but the clinical course may rule out sarcoidosis. At
the time of second admission, PSS-IP was inactive because of
end stage, but the clinical course may rule out sarcoidosis. At
judging from the above data, at least seven cases have been
reported. These results suggest the existence of a relationship
between PSS and sarcoidosis.

References

1) James DG, Williams WJ. Immunology of sarcoidosis. Am J Med 72: 5,
1982.
2) Needleman SW, Silber RA, Von Brecht JH, Goeken JA. Systemic lupus
erthematous complicated by disseminated sarcoidosis. Report of a case
associated with circulating immune complexes. Am J Clin Pathol 78: 105,
1982.
3) Rubinstein I, Baum GL, Hess Y, Margaliot S, Yellin A. Sarcoidosis and
Hashimoto’s thyroiditis – a chance occurrence? Respiration 48: 136,
1985.
4) Karlish AJ, MacGregor GA. Sarcoidosis, thyroiditis and Addison’s
5) Spitzer T, Crum E, Schacter L, Abboud S. Sarcoidosis, Hodgkin’s
disease, and autoimmune hemolytic anemia. Am J Med Sci 291: 190,
1986.
6) Lawrence HJ, Greenberg BR. Autoimmune thrombocytopenia in sar-
7) Schneider RM, Worsley A, Lichtman S, Meyer RJ. Sarcoidosis with
immune hemolytic anemia and thrombocytopenia: humoral aberrations
8) Fallahi S, Collins RD, Miller KK, Halla JT. Coexistence of rheumatoid
arthritis and sarcoidosis: difficulties encountered in the differential
9) Maekawa Y, Nogami R. A case of progressive systemic sclerosis associ-
ated with sarcoidosis and esophageal adenocarcinoma. J Dermatol 20: 45,
1993.
10) Teilm G. Pathogenetic studies on lupus erythematosus disseminatus and
11) Bara J, Marche J, Netter JC, Hugues FC, Achache S, Orvoën E. Syndrome
de Gougerot-Sjögren révélateur d’une sclérodermie et d’une maladie de
12) Wiesenhutter CW, Sharma OP. Is sarcoidosis an autoimmune disease?
Report of four cases and review of the literature. Semin Arthritis Rheum
13) Yagura T, Shimizu M, Yamamura Y, Tachibana T. Serum IgE levels and
reaginic-type skin reactions in sarcoidosis. Clin Exp Immunol 21: 289,
1975.
14) Horwitz DA, Garrett MA. Lymphocyte reactivity to mitogens in subjects
with systemic lupus erythematosus, rheumatoid arthritis, and sclero-
15) Hughes P, Holt S, Rowell NR, Allomby JD, Janis K, Dodd JK. The
relationship of defective cell-mediated immunity to visceral disease in
16) Daniele RP, Rowlands DT Jr. Lymphocyte subpopulations in sarcoidosis:
correlation with disease activity and duration. Ann Intern Med 85: 593,
1976.
17) Poulter LW. Immune aspects of sarcoidosis. Postgrad Med J 64: 536,
18) Crystal RG, Reynolds HY, Kalica AR. Bronchoalveolar lavage: the
19) Clinical guidelines and indications for bronchoalveolar lavage (BAL): report
of the European Society of Pneumology Task Group on BAL. Eur
20) Takehara K, Iizumi K, Mori S. Epidemiological study on systemic
scleroderma in Tokyo based on application forms for financial aids for the
patients with intractable diseases. Annual report of ministry of health and
21) Hiraga Y. Sarcoidosis subcommittee report. Annual report of ministry of
health and welfare, diffuse lung disease committee Japan: 17, 1996 (in
Japanese).