Sarcoidosis with Multiple Organ Involvement Emerging as Löfgren’s Syndrome

Miki OSHIMA, Hiroyuki MAEDA, Osamu FURONAKA, Masao DOI, Takashi NISHIZAKA* and Masao KUWABARA

Abstract

A 52-year-old woman was admitted because of high-grade remittent fever, erythema nodosum, and arthritis which had been lasting two months. Antibiotics did not improve her condition. A chest CT scan examination revealed bilateral hilar and mediastinal adenopathy and multiple nodular opacities in the bilateral lungs. The wedge biopsy of the right lower lobe using video-assisted thoracoscopy presented the histological findings of sarcoidosis. Finally, this case fulfilled the criteria of Löfgren’s syndrome. Due to the uncovered cardiac involvement, the systemic glucocorticoid therapy had to be initiated. This case suggests that atypical forms of sarcoidosis including Löfgren’s syndrome should be considered as a cause of unknown fever, though rare in Japan.

Key words: erythema nodosum, arthritis, high-grade remittent fever, bilateral hilar lymphoma, video-assisted thoracoscopy, cardiac involvement

Introduction

Sarcoidosis is a multisystemic granulomatous disorder of unknown etiology presenting most frequently with bilateral hilar lymphadenopathy (BHL), pulmonary infiltration and skin or eye lesions. In Japan, most cases of sarcoidosis have been discovered at regular health checkups, however, the number of cases found after subjective or objective symptoms are increasing (1). Among a variety of disease-types, Löfgren’s syndrome (2, 3), an acute form of sarcoidosis with erythema nodosum, arthritis, and BHL, is extremely rare in Japan, of which only two cases have been reported to date (4).

We describe a case of sarcoidosis with multiorgan-involvement which emerged as Löfgren’s syndrome. The video-assisted thoracoscopy (VATS) was useful for the diagnosis, which lead to the necessary treatment for the asymptomatic cardiac lesion. This case suggests that atypical forms of sarcoidosis including Löfgren’s syndrome should be considered as a cause of unknown fever, though rare in Japan.

Case Report

A 52-year-old woman was admitted because of high-grade remittent fever, erythema nodosum on the left tibial leg, polyarthritis in the bilateral knees and ankles, body weight loss, and blunt vision which had been lasting two months. The laboratory findings on admission revealed mild leukocytosis (4,900/μl), elevated C-reactive protein (2.3 mg/dl), microcytic anemia (hemoglobin 10.6 g/dl), negative purified protein derivative (PPD) skin test, and a normal serum angiotensin-converting enzyme (ACE) level (17.4 IU/l). Tumor markers including carcinoembryonic antigen (2.5 ng/ml) and neuron-specific enolase (10.1 ng/ml) were not elevated. HLA class I antigen analysis revealed the presence of HLA-A31, 33, B51, 44, DR4. But the immune complex was not measured. Extensive blood, sputum, and urine cultures were negative for pathogenic microorganism. No obvious abnormalities were detected except for bilateral inflammatory granular shadows by chest X-ray (Fig. 1). An electrocardiogram revealed the second-degree atrioventricular block Mobitz type 2. Bone and joint X-Ps of the left tibial legs were normal. Initially, despite lacking definitive evidence, broad spectrum-antibiotics were administered with concern about infectious diseases. High-grade fever did not improve, while EN and arthritis disappeared shortly after the initiation of the treatment (Table 1). A chest CT
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scan (Fig. 2) revealed bilateral hilar and mediastinal lymphadenopathy and multiple nodules in bilateral lungs, which were not detectable by the plain X-Ps (Fig. 1). A wedge biopsy of the right lower lobe was performed by VATS. Histopathological examination of the resected specimens demonstrated intrapulmonary lymph nodes with non-caseating granulomas which were composed of clustered epitheloid histiocytes, multinucleated giant cells with lymphocytes or other inflammatory cells (Fig. 3), typical histological findings of sarcoidosis. As a result, this case fulfilled the criteria of Löfgren’s syndrome. Further medical analyses were then carried out for the evaluation of systemic involvement of sarcoidosis. Gallium-67 ($^{67}$Ga) scintigraphy showed abnormal uptake in neck, hilar and mediastinal lymph nodes, heart and parotid glands. The bronchoscopy findings revealed network formation of capillary vessels on the mucous membrane of the main bronchus and bronchi. Bronchoalveolar lavage (BAL) revealed increases in the total cell number ($4.6 \times 10^5$/ml), the lymphocyte cell number (47%), and the ratio of CD4/CD8 cells (8.3). The spirometry (FVC 2.71, FEV$_1$ 2.41) and arterial blood gas analysis (pH 7.4, PaCO$_2$ 36, PaO$_2$ 85, SaO$_2$ 98%) were normal except for the slight reduction of the diffusing capacity for carbon monoxide to 66%. Although an echocardiogram showed normal left ventricular function, exercise-loaded thallium-201 ($^{201}$Tl) myocardial imaging revealed perfusion abnormalities in the anteroseptal region in the initial images and redistribution in the delayed image. Both $^{67}$Ga and technetium-99m pyrophosphate ($^{99m}$Tc-pyp) scintigraphy revealed abnormal uptake in

**Figure 1.** Chest X-ray did not reveal any obvious abnormalities, except for bilateral inflammatory granular shadows.

**Table 1. Clinical Course**

<table>
<thead>
<tr>
<th>May</th>
<th>June</th>
<th>July</th>
<th>August</th>
</tr>
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<tbody>
<tr>
<td>Admission</td>
<td>VATS</td>
<td></td>
<td>Discharge</td>
</tr>
<tr>
<td>Antibiotics</td>
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<td></td>
<td>Prednisolone</td>
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<tr>
<td>Arthritis</td>
<td>erythema nodosum</td>
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<td>25 mg/day</td>
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<table>
<thead>
<tr>
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<th>CRP</th>
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<tbody>
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<table>
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<th>FVC</th>
<th>FEV$_{1,0}$</th>
<th>%DLco</th>
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<tbody>
<tr>
<td>19.0 IU/l</td>
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<td>17.4 IU/l</td>
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<tr>
<td>12.7 IU/l</td>
<td>7.3 μg/ml</td>
<td>2.41 l (88.3%)</td>
<td>66.8%</td>
</tr>
<tr>
<td>12.1 IU/l</td>
<td>5.4 μg/ml</td>
<td>2.36 l (86.1%)</td>
<td>76.3%</td>
</tr>
</tbody>
</table>

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A

B

Figure 2. Chest computed tomographic scan revealed bilateral hilar and mediastinal adenopathy (A) and multiple nodular opacities in the bilateral lungs (B).

A

B

Figure 3. Wedge biopsy specimen using VATS demonstrated intrapulmonary lymph nodes with non-caseating granulomas (A) and granulomas composed of epithelioid histiocytes, multinucleated giant cells with lymphocytes or other inflammatory cells (B) (HE stain, ×200).

A

B

Discussion

The triad of Löfgren’s syndrome consists of EN, BHL and arthritis, which heralds the acute onset of sarcoidosis (2, 3). The incidence of the syndrome varies according to country and race. In Europe and United States, approximately 10% of the patients with sarcoidosis presents with Löfgren’s syndrome, who are mainly white young women with anceseral origin particularly from the Nordic countries and Ireland, whereas it is uncommon in blacks (3). In Japan, the frequency of the patients with the syndrome is extremely rare (4, 5). The syndrome is closely related to HLA-B8 and DR3 in Caucasians (5–8), to which antigens other autoimmune diseases have been related as well (5). In the present case, however, neither antigen was positive. Interestingly, the frequency of HLA-B8 and DR3 in Japanese is very rare (5), which may affect the low prevalence of this syndrome in Japan. When sarcoidosis presents as Löfgren’s syndrome, the prognosis is generally favorable with complete remission within two years in more than 90% cases (2, 9). Indeed, this syndrome is generally a self-limiting disease, becoming inac-
tive within the first year (3). However, some authors have noted that some patients with this syndrome develop chronic sarcoidosis (10). In the present case, skin and joint lesions disappeared in three months after onset. Our case was described as an atypical form of sarcoidosis with chronic multiple organ involvement, which emerged as Löfgren’s syndrome. However, the clinical course should be followed up carefully, because cardiac involvement is responsible for as many as 85% of deaths from sarcoidosis (11).

In the present case, the atypical chest X-P findings and normal serum level of ACE made the clinical diagnosis of sarcoidosis rather difficult. Because the heart had completely shaded the bilateral hilar and mediastinal lymphadenopathy, the BHL could not been detected. The serum ACE levels are reported to be increased at diagnosis only in half of the pa-
tients with Löfgren’s syndrome (3). In this regard, the histological evaluation was essential for the diagnosis of this
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The usefulness and safety of lung biopsy using VATS in diagnosing sarcoidosis, tuberculosis, IPF and collagen lung has been described (12, 13). In the present case, the VATS was useful for the diagnosis, which finally lead to the necessary treatment for the asymptomatic cardiac lesion.

This case suggests that atypical forms of sarcoidosis including Lofgren’s syndrome should be considered as a cause of unknown fever, though rare in Japan.

References