Antisynthetase Syndrome Associated with Sarcoidosis

Yu Asanuma¹, Reiko Koichihara¹, Shinichiro Koyama¹, Yoshinori Kawabata², Shio Kobayashi³, Tsuneyo Mimori³ and Masato Moriguchi¹

Abstract

A 30-year-old man complained of polyarthritis and fatigue. The clinical findings and laboratory data included myositis, polyarthritis, interstitial pneumonia, Raynaud’s phenomenon, mechanic’s hand, and anti PL-7 antibody (threonyl-tRNA synthetase antibody). All of these signs were consistent with antisynthetase syndrome. His chest radiograph revealed bilateral hilar lymphadenopathy. Biopsy specimens from his mediastinal lymph node and muscle showed noncaseating epithelioid cell granulomas. Lung histology revealed nonspecific interstitial pneumonia. Antisynthetase syndrome associated with sarcoidosis was diagnosed. Interstitial pneumonia in this patient responded well to high-dose corticosteroid therapy.

Key words: sarcoidosis, antisynthetase syndrome, interstitial pneumonia

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Case Report

A 30-year-old man who was a heavy smoker visited our hospital complaining of polyarthritis and fatigue. He had experienced Raynaud’s phenomenon, dry cough, and dyspnea on exertion since he was 23 years old. Extensive edema of the fingers developed at the age of 24. For 6 months before admission, he suffered from joint swelling and tenderness of both his hands and knees.

After admission, physical examination revealed a body temperature of 37.2°C, blood pressure of 110/70 mmHg, and a pulse rate of 84 beats per minute with a regular rhythm. He had erythematous rash over his eyelids (heliotrope rash) and forehead, and scleroderma on both sides of his forearms and hands. He also had roughened lateral and palmer surfaces of his index fingers. There was no swelling of superficial lymph nodes. Chest auscultation and abdominal examination were normal. White blood cell count was 6,300 cells/µL. Inflammatory markers such as erythrocyte sedimentation rate (56 mm/h) and C-reactive protein (3.11 mg/dL) were elevated. Serum creatine kinase level was elevated to 520 IU/L. Rheumatoid factor and antinuclear antibody were negative but anticytoplasm antibody was positive. Anti Jo-1, anti Scl-70, and anti-RNP antibodies were all negative. Serum levels of angiotensin-converting enzyme and lysozyme were within the normal range. Serum levels of KL-6 and SP-D were 374 U/ml and 243 ng/ml, respectively.

Chest radiographs revealed bilateral hilar lymphadenopathy with some pulmonary interstitial change. Chest computed tomography showed bilateral ground glass opacities in the lower lungs (Fig. 1). The purified protein derivative skin test was negative. A pulmonary function test showed reduction of vital capacity and Dco (VC 3.23 L, %VC 79.8%; %Dco 62.2%). A muscle biopsy of the quadriceps femoris showed noncaseating epithelioid cell granulomas (ECG) within the perimysial connective tissue and endomysium (Fig. 2). Muscle fiber degeneration suggesting patchy myopathic change was also seen. A forearm skin biopsy showed excess collagen deposition in the dermis that was compatible with scleroderma. Histopathologic findings from the lung tissue and lymph node were obtained from tissue collected by video-assisted thoracoscopic surgery. The lung specimen showed widening of the alveolar septa by loose collagenous fibrosis and active fibrotic lesions with lymphoctic infiltration in the alveolar wall. Partly, there was small granuloma formation (Fig. 3-a). The biopsy specimen from the mediastinal lymph node revealed confluent noncaseating

¹ Clinical Department of Internal Medicine, Jichi Medical School Omiya Medical Center, Saitama, ² Department of Pathology, Saitama Prefecture Cardiovascular and Respiratory Center, Saitama and ³ Department of Rheumatology and Clinical Immunology, Graduate School of Medicine, Kyoto University, Kyoto

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Correspondence to Dr. Yu Asanuma, Division of Rheumatology and Applied Immunology, Department of Medicine, Saitama Medical School, 38 Morohongo, Moroyama-machi, Iruma-gun, Saitama 350-0495
ECG (Fig. 3-b). These histopathological findings were summarized as nonspecific interstitial pneumonia (NSIP) and sarcoid granulomas.

Antisynthetase antibody was measured in the serum of this patient by the immunoprecipitation method described previously (1). The serum was found to be positive for anti PL-7 antibody by precipitating a unique tRNA that was identical with anti PL-7 reference serum (Fig. 4). Other antibodies including anti-OJ, anti-EJ, anti-PL12 and anti-KS were not identified.

A high dose of corticosteroid (1 mg/kg of prednisolone) was administered for the treatment of interstitial pneumonia. After corticosteroid therapy was started, the values of vital capacity and D.co were recovered (%VC, 83.3%; %D.co, 87.7%). Radiograph findings of NSIP and hilar lymphadenopathy were improved. Polyarthritis was reduced, and serum creatine kinase level was decreased to within the normal range. No evidence of recurrence has been observed in this patient after tapering of corticosteroid to under 10 mg/day.

Discussion

Antibodies against aminocyl transfer RNA (tRNA) synthetases are myositis-specific autoantibodies that are found in 25-30% of patients with polymyositis (PM)/dermatomyositis (DM) (2). Aminocyl-tRNA synthetases are cytoplasmic enzymes that catalyze the binding of amino acids to their cognate tRNAs. Seven autoantibodies directed against synthetases have been described. A subgroup of inflammatory myopathies characterized by the presence of antisynthetase antibodies was called the antisynthetase syndrome (2). Patients with antisynthetase syndrome have a high prevalence of interstitial lung disease, fever, polyarthritis, Raynaud’s phenomenon, and thick cracked skin over the tips and sides of the fingers (mechanic’s hands) (3). An overlap syndrome with scleroderma is also seen in antisynthetase syndrome. Anti PL-7 antibody (anti-threonyl tRNA synthetase antibody) is detected in 2% of patients with PM/DM (4, 5). Anti PL-7 has been reported to be associated with interstitial lung disease, Raynaud’s phenomenon, and arthritis (6).

Because the present patient had heliotrope rash, proximal
Figure 4. Identification of anti-PL-7 antibody in patient serum by RNA-immunoprecipitation. Serum (10 μL) was incubated with protein A-sepharose beads (2 mg) in a buffer, and IgG-coated beads were then incubated with HeLa cell extracts (6×10^6 cells). Immunoprecipitated RNAs on the beads were extracted with phenol-chloroform, separated on a 8M urea-15% polyacrylamide gel, and visualized by silver staining as described previously (1). Total HeLa cell RNAs (lane 1) and immunoprecipitated tRNAs from reference sera containing known anti-aminoacyl-tRNA synthetases are shown on the same gel (lanes 2-7). The patient's serum (lane 8) contains anti-PL-7 antibody, since it immunoprecipitates the identical tRNA with that from anti-PL-7 reference serum (lane 7).

scleroderma, Raynaud’s phenomenon, and elevated serum creatine kinase, we first thought he had an overlap syndrome of DM and systemic sclerosis. He also had interstitial pneumonia, polyarthritis, and mechanic’s hands. Those findings are consistent with clinical features of antisyndrome; and in fact, this patient had anti PL-7 antibody. Anti-PL-7 antibody in this patient serum was detected by RNA-immunoprecipitation although we did not identify this antibody by SDS-PAGE.

In general, myopathy is developed in both antisynthetase syndrome and sarcoidosis (7). The muscle and lymph node specimens from the present patient showed noncaseating ECG. Pathological findings from muscle specimens in antisynthetase syndrome commonly include fragmentation of perimysial connective tissue, macrophage predominant perimysial inflammation, and perifascicular myopathic change in regions near connective tissue pathology (8). We concluded that the myopathy of this case was due to systemic sarcoidosis.

Sarcoidosis, a systemic granulomatous disorder of unknown etiology, is rarely complicated with connective tissue diseases such as DM (9-11) or systemic sclerosis (12). Because such patients have various symptoms and signs, it is difficult to distinguish whether their myopathy is caused by sarcoidosis or connective tissue disease. Histopathological findings from muscle are useful to determine a cause of myopathy in patients with systemic sarcoidosis accompanied by inflammatory myositis. The presence of interstitial lung disease is an important prognostic factor of antisynthetase syndrome (3, 13). Corticosteroid and immunosuppressant are usually administered for the treatment of interstitial lung disease in antisynthetase syndrome. The present patient had a good response to high-dose corticosteroid therapy.

Clinical findings and biopsy specimens from skin and lung of this patient suggested antisynthetase syndrome with systemic sclerosis, whereas pathological findings from lymph node and muscle were consistent with sarcoidosis. The findings of this patient related to antisynthetase syndrome were polyarthralgia, Raynaud phenomenon, mechanic’s hand (scleroderma) and positive for anti-PL-7 antibody. According to the biopsy specimens of muscle and lymph node, myositis and bilateral hilar lymphadenopathy of this case were related to sarcoidosis. The lung specimen showed mainly NSIP but partly small granuloma formation that might be due to manifestations of antisynthetase syndrome and/or sarcoidosis. The characteristic feature of this patient is that each of the diseases affected multiple organ systems in a mosaic pattern. Sarcoidosis is regarded as an immunologic disorder because CD4-positive T cells participate as the central mediators in initiating and building the granuloma (14). Various cytokines and chemokines contribute to the pathogenesis of sarcoidosis (15). Thus, sarcoidosis might have coexisted with antisynthetase syndrome under immune-mediated disorder in this patient.

References