A Case of Adult Onset Still’s Disease Complicated with Cryptogenic Organizing Pneumonia

Hiroshi Sato¹, Isamu Yokoe¹, Shinya Nishio¹, Tsubasa Onishi¹, Tadashi Takao², Yasuyuki Kobayashi³ and Hitomi Haraoka¹

Abstract

Only a few pathologic reports exist describing adult onset Still’s disease (AOSD) with pulmonary involvement. We report this very rare case of AOSD complicated with cryptogenic organizing pneumonia (COP). A 32-year-old woman was referred with high spiking fever, salmon-pink rash in her arms and legs, and polyarthralgia. The laboratory data showed marked increases in white blood cell count, an erythrocyte sedimentation rate, and C reactive protein, ferritin, and liver dysfunction. All cultures remained negative, as were autoantibodies and rheumatoid factor. The patient was strongly suspected of AOSD according to specific diagnostic criteria. However, chest X ray disclosed an infiltrative shadow accompanied by air bronchogram in the upper lobe of the right lung and therapy with antibiotics was initiated. As the patient did not respond to antibiotics and a remittent fever of over 38°C, a flexible bronchoscopy was performed. Organizing pneumonia was diagnosed by transbronchial lung biopsy (TBLB) histology and radiologically, and the lesions were thought to be due to pulmonary involvement of AOSD. Therefore, she was diagnosed with AOSD complicated with COP. Oral treatment with prednisolone (30 mg/day) resulted in rapid disappearance of the infiltrative shadow. Symptoms and markers of inflammation also improved. Clinicians should be aware that COP can be a complication of AOSD.

Key words: adult onset Still’s disease, cryptogenic organizing pneumonia

(Intern Med 50: 247-251, 2011)
(DOI: 10.2169/internalmedicine.50.4180)

Introduction

Adult onset Still’s disease (AOSD) is the rare clinical condition characterized by high spiking fever, evanescent macular or maculopapular rash, poly- or oligoarthritis and leucocytosis (1). About 30 percent of AOSD patients are reported to have pulmonary involvement such as pleuritis and transient radiographic infiltrations (2). Cryptogenic organizing pneumonia (COP) is an interstitial lung disease characterized by intra-alveolar buds of connective tissue (3). It can be idiopathic or associated with a known underlying disease. Although connective tissue diseases have been known to induce COP, AOSD has only rarely been etiologically associated with COP. We recently encountered a patient with AOSD whose transbronchial lung biopsy (TBLB) showed the typical signs of organizing pneumonia. We report a case which may be suggestive of pathophysiological mechanisms when considering the conditions of both diseases.

Case Report

A 32-year-old woman suffered from spiking fever, rash, and polyarthralgia for about 2 weeks prior to admission. Her family history and clinical history were unremarkable. She first felt febrile on in early December 2009, and, at the same time, a salmon pink rash appeared on bilateral forearms. She consulted with dermatology at another hospital and was diagnosed with urticaria and prescribed an ointment. Two days later, polyarthralgia developed, affecting mainly her left shoulder and knees. She visited the outpatient clinic at our hospital three weeks later. At that time, intense inflamma-
tory reactions were noted and she was hospitalized. On admission, her body temperature was 38.2°C, heart rate 88/min, blood pressure 111/72 mmHg and SpO2 98% (room air). Her palpebral conjunctiva showed no signs of anemia. Her ocular conjunctiva showed no abnormal changes. Chest auscultation revealed no abnormality. Her wrist joints and ankle joints showed marked swelling and tenderness, but no sign of muscular weakness or atrophy was noted. White cell blood count was 93x10^3/μL (neutrophilia 93.5%, lymphocyte 6%), erythrocyte sedimentation rate was as high as 101 mm/hr. Mild liver dysfunction [aspartate aminotransferase (AST) 6%], erythrocyte sedimentation rate was as high as 101 mm/hr. Mild liver dysfunction [aspartate aminotransferase (AST) 52 U/L, alanine aminotransferase (ALT) 46 U/L] were noted, the ferritin level was high (505.1 ng/mL) and C-reactive protein (CRP) was markedly elevated (35.49 mg/dL). No elevation was seen in anti-streptolysin O antibody and anti-cyclic citrullinated peptides (CCP) antibody were both negative. Rheumatoid factor, antinuclear antibody and anti-cyclic citrullinated peptides (CCP) antibody were negative, and antineutrophilic cytoplasmic antibody (ANCA) was negative. Urinalysis revealed no abnormality. Chest X ray revealed infiltrative shadow accompanied by air bronchogram in the right lung upper lobe (Fig. 1). Electrocardiography disclosed no abnormality. During hospitalization, remittent fever (38-39°C) was noted. All cultures were negative. Aspergillus antigen and beta-D glucan were all negative. Liver dysfunction, polyarthritis, salmon pink rash (seen during fever), and elevation of inflammation parameters were noted. She was diagnosed with AOSD according to Yamaguchi diagnostic criteria (4). However, an infiltrative shadow accompanied by air bronchogram was seen in the upper lobe of the right lung in the chest X ray obtained on admission, and chest computed tomography (CT) findings on admission revealed the consolidation at the right S1 partially surrounded by ground glass opacity (Fig. 2a, 2b). Bacterial pneumonia was also considered and therapy with 2 g flomoxef sodium (FMOX) was initiated. Despite continued treatment with the antibiotic, fever and arthritis persisted and inflammatory reactions remained elevated. The tuberculin reaction was negative, CEA was 2.7 ng/mL, Pro-GRP was 13.5 pg/mL, CYFRA was <1.0 ng/mL, and KL6, SP-D and SP-A were within normal range. As chest X ray abnormalities were thought to be indicative of pulmonary involvement of AOSD, a flexible bronchoscopy was performed. Bronchoalveolar lavage (BAL) and bronchial brush specimens were negative in both the acid-fast smear test and culture. Polymerase chain reaction (PCR) of tubercle bacillus was also negative. BAL and brush specimen were rated as class I and II in cytology. BAL showed lymphocyte-predominant with no eosinophils and neutrophils (CD4 was 47.6%, CD8 was 41.4% and CD4/CD8 ratio was 1.15). Histological examination of the TBLB specimen disclosed lymphoplasmacytic inflammatory infiltration on bronchial wall indicated and faintly-stained intra-alveolar organization indicated, without pulmonary alveolitis and fibrosis in Elastica van Gieson (EVG) stain, confirming the diagnosis of organizing pneumonia (Fig. 3). Based on these results, malignant disease and infection such as tuberculosis were considered unlikely, and the patient was diagnosed AOSD complicated with organizing pneumonia. Consequently, oral treatment with prednisolone (30 mg/day) was started on the 12th hospital day. On the 13th hospital day, fever subsided and arthralgia alleviated. Blood collected on the 16th hospital day revealed a decrease of CRP to 3.08 mg/dL. On the 23rd day, follow-up chest CT scans revealed marked reduction of the lesion in the upper lobe of the right lung (Fig. 4). On the 25th hospital day, the dose of prednisolone was reduced to 25 mg/day. The patient did not show a relapse of symptoms thereafter and was discharged on the 30th hospital day.

Discussion

The frequency of pulmonary manifestations in AOSD is reported to be 12-53% for pleuritis and 0-27% for interstitial pneumonia (4, 5). Pleuritis is often seen soon after onset of AOSD or during acute exacerbation of AOSD. Interstitial pneumonia is acute and it is detected as a transient infiltrative shadow. Histopathologically, it shows signs of acute interstitial pneumonia, sometimes accompanied by partial fibrosis. Signs of angitis are absent (6). Previous reports of patients with chronic persistent interstitial pneumonia detected by TBLB, indicate lymphocyte infiltration and mild fibrosis of the alveolar wall (7-9). Recently, Hijikata et al reported a case of AOSD in which TBLB revealed a pattern of organizing pneumonia (10). However, cases of AOSD presenting pulmonary manifestation detected by TBLB or BAL are quite rare.

COP, the idiopathic form of organizing pneumonia, is a distinct clinical entity with predominant features of pneumonia, rather than a primary airway disorder (11). In the international classification of interstitial pneumonia prepared by

Figure 1. An irregular-shaped infiltrative shadow is seen in the right upper lung, measuring 1.5 cm in diameter.
American Thoracic Society/European Respiratory Society (ATS/ERS) in 2002, COP was adopted as one of the 7 types of idiopathic interstitial pneumonia (12). Since then, the term COP has been widely recommended as a substitute for the previously used bronchiolitis obliterans with organizing pneumonia (BOOP). This is because organizing pneumonia primarily affects the lung parenchyma (the alveolar duct and surrounding tissue) rather than the bronchioles. Pathologically, the primary lesion of organizing pneumonia (intracavitary organizing change of the lung parenchyma) is a nonspecific lesion and similar lesions can appear in the presence of diverse lung diseases. Thus, the diagnosis of COP requires a general assessment of various findings, including clinical symptoms and findings from diagnostic imaging (13). The

three main characteristic CT imaging patterns of COP consist of multiple alveolar opacities (typical COP), solitary opacity (focal COP), and infiltrative opacities (infiltrative COP) (14). The three types are as follows: [1] Typical COP; multiple alveolar opacities on imaging represent the most frequent and typical imaging features of COP. These are usually bilateral and peripheral, and are often migratory. Their size varies from a few centimeters to a whole lobe, and an air bronchogram is often present in consolidated opacities. [2] Solitary focal opacity; this pattern is not characteristic and the diagnosis of COP is often made from histopathology of a nodule or a mass excised on suspicion of bronchogenic carcinoma (15, 16). However, organizing pneumonia is distinct from pneumonia which improves with antibiotics. The lesions are often located in the upper lobes. The clinical presentation may be that of COP as described above, but focal organizing pneumonia may be totally as-
ymptomatic and discovered by routine chest radiographs (17). [3] Infiltrative COP; Infiltrative COP is often associated with interstitial and superimposed small alveolar opacities on imaging. Some cases overlap with other types of idiopathic interstitial pneumonias (IPF), especially IPF and nonspecific interstitial pneumonia (NSIP). In the latter, focal areas of organizing pneumonia are often encountered at histopathology (18). The radiographic findings of the present case showed solitary focal opacity and the patient had no respiratory symptoms.

A major pathological finding is defined histopathologically by intra-alveolar buds of granulation tissue, consisting of intermixed myofibroblasts and connective tissue (19). However, this organizing pneumonia is the most important process underlying the clinical and radiographic manifestations of COP.

In the present case, no sign of flu or other respiratory symptom preceded the sudden onset of fever, and the salmon pink rash appeared only during high fever, accompanied by arthralgia prior to the onset of AOSD. It seemed unlikely that bacterial pneumonia or any other infection had developed in advance and induced AOSD in this patient. Therefore, based on a general assessment of the clinical course, findings from CT images and histopathological findings obtained from BAL and TBLB, this patient was diagnosed with AOSD complicated with COP.

The etiology of COP is currently unknown and still has not been confirmed. The report stating that COP has a good response to corticosteroids and that alveolitis is T-cell oriented has suggested some involvement of an immunological mechanism (20). COP has been described in various autoimmune diseases; in rheumatoid arthritis (21), systemic lupus erythematosus (22), polymyositis/dermatomyositis (23) and scleroderma (24). However, the association of COP with AOSD is extremely rare. On the other hand, more recently, it has been suggested that alterations in cytokine production and pathophysiological role in AOSD. Although the simultaneous onset of AOSD and COP suggests some autoimmune mechanism, further research is needed to confirm or disconfirm our hypothesis.

Treatment of AOSD is focused either on the systemic or articular disease. Systemic disease would initially depend on corticosteroids to achieve rapid control of a sick patient. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be effective in a few patients, but most with a firm diagnosis of AOSD will initially require prednisone of 30-60 mg. COP accompanying collagen disease often responds well to corticosteroid therapy. When corticosteroids are used for the treatment of COP, prednisolone (PSL) is administered at a dose of 0.5-1 mg/kg for 4-8 weeks (25, 26). Therefore, the patient was started on 30 mg (0.5 mg/kg) of PSL due to moderate AOSD activity and COP complication. The symptoms and inflammatory reactions alleviated rapidly after the start of this therapy, and the symptoms did not return despite gradual reduction of the dose level every other week.

In summary, we encountered a case of AOSD with COP that proved to be organizing pneumonia on the basis of CT and pathologic findings of TBLB. This report describes an association between COP and AOSD, which suggests that similar pathophysiological mechanisms may be present in some patients with these disorders. Further data and information about pulmonary involvement in patients with AOSD should be collected in the future.

The authors state that they have no Conflict of Interest (COI).

References


© 2011 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imindex.html