A Rare Case of Diffuse Pulmonary Nodules in a Patient with Adult-onset Still’s Disease

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Abstract

Adult-onset Still’s disease (AOSD) is a multisystemic inflammatory disorder, but pulmonary involvement is rare. We herein describe the case of a woman diagnosed with AOSD; treatment resolved her symptoms, but nine days later she was admitted with pyrexia and a productive cough. A chest X-ray revealed diffuse pulmonary nodules and patchy shadows. A high-resolution chest computed tomography scan confirmed diffuse infiltration in the pulmonary parenchyma, signs of alveolar nodules, distribution along the lobule center, several areas of tree-in-bud patterns, and bilateral pleural effusion. The patient was treated with high doses of corticosteroids, which rapidly reduced the size of her diffuse pulmonary nodules and dramatically improved her pleural effusion.

Key words: adult-onset Still’s disease (AOSD), pulmonary nodules, diagnosis

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Introduction

Adult-onset Still’s disease (AOSD) is a multisystemic inflammatory disorder of unknown origin. The pathogenesis of AOSD is characterized by a high spiking fever, an evanescent salmon-pink rash, and arthritis. AOSD is also frequently accompanied by sore throat, myalgias, lymphadenopathies, splenomegaly, and neutrophilic leukocytosis. The erythrocyte sedimentation rate is consistently high in patients with AOSD, and assessments for rheumatoid factors and antinuclear antibodies are negative. High serum ferritin levels are useful for diagnosing AOSD and assessing disease activity. Pulmonary involvement is rare, but the exact incidence is unclear. The most common pulmonary manifestations of AOSD are transient pulmonary infiltrates and pleural effusion (1).

Case Report

A 22-year-old woman was admitted with a one-month history of intermittent fever and rash and reported multi-joint swelling and pain lasting 15 days. There was no throat sore or cough. She did not smoke, did not have pets, and had no recent travel or contact history. She had a temperature of 39°C, pink maculopapular eruption, arthritis in the left knee and right wrist, cervical and inguinal lymph node enlargement, and splenomegaly. Her hemoglobin was 95 g/L, her leukocyte count 18,000/μL, her complete blood count revealed 80.3% neutrophils, and she had a high erythrocyte sedimentation rate (96 mm in the first hour). Her C-reactive protein level was high (38 mg/L), and her liver enzymes were elevated: aspartate aminotransferase (47 U/L) and alanine aminotransferase (90 U/L). The assays for antinuclear, anti-dsDNA, anti-cyclic citrullinated peptide, anti-U1 ribonucleoprotein (RNP), anti-Scl-70, and anti-neutrophil cytoplasmic antibodies were all negative. Her rheumatoid factor and anti-streptolysin O titers were within the normal range. Because the Yamaguchi diagnostic criteria (2) for AOSD were fulfilled, a serum ferritin estimation was performed, and it was found to be elevated (1,605 ng/mL). She was started with oral loxoprofen 60 mg three times per day, and her temperature normalized, the rash disappeared, and her joint symptoms were relieved.

However, nine days later she again presented with pyrexia with a productive cough; white phlegm expectorate, polypnea; and no hemoptysis, thoracalgia, or cyanosis. Her chest auscultation revealed no specific signs. Her aspartate

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aminotransferase and alanine aminotransferase levels were further increased to 404 U/L and 703 U/L, respectively. An electrocardiogram and echocardiogram revealed no cardiac function abnormalities. A chest X-ray revealed bilateral diffuse pulmonary nodules and pleural effusion (Fig. 1A). A high-resolution chest computed tomography (HRCT) scan confirmed diffuse infiltration in the pulmonary parenchyma, alveolar nodules, distribution along the lobule center, several areas of tree-in-bud patterns, bilateral pleural effusion (Fig. 1B), and mediastinal lymph node enlargement. However, her chest X-ray from nine days earlier was normal.

An ultrasound of the abdomen showed moderate hepatomegaly. The following tests were negative: human immunodeficiency virus (HIV); hepatitis B and C; adenovirus serotypes 3, 7, and 11; rubella virus; Epstein-Barr virus; herpes simplex viruses 1 and 2; Coxsackie virus; and cytomegalovirus. All of the patient’s smear and culture reports for urine, sputum, and blood were negative. Her pleural fluid proved to be exudative, and the proportion of monocytes was 80%.

Due to her radiological manifestation of diffuse nodules and bilateral plural effusion, we performed almost all tests for tubercle bacillus (TB). A sputum smear and pleural effusions were negative in the acid-fast smear test, culture, and polymerase chain reaction (PCR) for TB. The tuberculin-purified protein derivate test was also negative. A Mycobacterium tuberculosis-specific ELISPOT (T-SPOT.TB) assay was performed, and the results were negative. The number of nucleated cells in the pleural effusion was 1,760×10⁶/L, and the percentages of mononuclear cells and multinucleate cells were 80% and 20%, respectively. Her adenosine deaminase level was within the normal range. Tests for rheumatoid factor and antinuclear antigen in her pleural effusion were both positive. Her serum angiotensin-converting enzyme level was normal.

As the patient’s clinical and radiological findings of the chest showed no signs of resolution after seven days of antibiotic treatment (moxifloxacin 400 mg per day intravenously for three days, followed by piperacillin/tazobactam plus etimicin sulfate for four days), a flexible bronchoscopy was performed. Bronchoalveolar lavage fluid (BALF) and bronchial brush specimens were negative in the routine bacterial culture, acid-fast smear test, culture, and PCR for TB. The fractions of all cells in the BALF were macrophages, 56%; lymphocytes, 12%; and neutrophil granulocytes, 32%. The ratio of CD4+ to CD8+ T-lymphocytes (CD4/CD8 ratio) in BALF was 2.8. An excision biopsy of one cervical lymph node did not show evidence of malignant lymphoma. A bronchoscopy brush biopsy was negative, and a pleural effusion smear was also free of tumor cells. A cytomorphologic examination revealed that her bone marrow was infectious, and culture and biopsy of bone marrow showed negative results. Her serum angiotensin-converting enzyme level was normal. The serum ferritin concentration of the patient climbed to 11,666 ng/mL.

The patient was given pulse intravenous methylprednisolone 500 mg/day for three days followed by oral prednisolone 40 mg/day, and all of her symptoms improved significantly. Signs of resolution of pneumonic changes were noted on chest HRCT performed at 11 days (Fig. 2); the patient’s bilateral pulmonary nodules were reduced, and her pleural effusion was dramatically improved. The patient’s neutrophilic leukocytosis and liver enzyme levels subsided, and her serum ferritin dropped to 6,400 ng/mL. Her C-reactive protein and erythrocyte sedimentation rate reduced to 20 mg/L and 60 mm/h, respectively. The prednisolone dosage was reduced stepwise in the following days. After three months of follow-up, the patient’s bilateral pulmonary nodules disappeared completely (Fig. 3). Her serum ferritin and C-reactive protein levels and erythrocyte sedimentation rate normalized. As of this writing, the patient has continued well with 15 mg oral prednisolone per day without any fur-
AOSD is a multisystemic inflammatory disorder, but pulmonary involvement is rare. The most common pulmonary manifestations of AOSD are pleural effusion and transient radiological pulmonary infiltrates, which may mimic pneumonia (3, 4). Pulmonary arterial hypertension (5, 6), cryptogenic organizing pneumonia (7), and diffuse alveolar hemorrhage (8) have also been described. Other severe pulmonary manifestations include adult respiratory distress syndrome and respiratory failure (9, 10). However, radiologically observed diffuse pulmonary involvement with centrilobular nodules and bilateral pleural effusion have not been described previously.

Our patient presented with a chronic fever and radiological manifestations of bilateral pulmonary nodules and pleural effusion. After excluding common etiologies, a diagnosis of AOSD was considered due to her fever of more than two weeks duration, polyarthritis, rash, persistent neutrophilic leukocytosis, and elevated liver enzymes. Hyperferritinemia and negative tests for anti-nuclear factor and rheumatoid factor further helped determine the patient’s diagnosis. Because there are no pathognomonic laboratory parameters for AOSD, the diagnosis requires the exclusion of infectious, malignant, and other autoimmune disorders.

Pleurisy is the most common clinical manifestation of pulmonary involvement in AOSD and can be associated with transient parenchymal infiltrates. Pleural biopsies performed in a limited number of patients have shown changes indicative of chronic nonspecific pleuritis without evidence of vasculitis (11). Transient acute parenchymal infiltrates involving the upper or lower lobes often accompany small pleural effusions. Transbronchial lung biopsy specimens from patients with AOSD have demonstrated changes indicative of acute pneumonitis with or without focal areas of fibrosis (11).

In the present case, HRCT confirmed diffuse infiltration in the pulmonary parenchyma, signs of alveolar nodules and distribution along the lobule center, several areas of tree-in-bud patterns, and bilateral pleural effusion; all of these findings reinforced support for effusion. The patient’s lung involvement rapidly resolved after glucocorticoid treatment, so we did not perform a lung biopsy. The signs of interstitial pneumonia on HRCT are ground-glass opacity, interlobular septal thickening, and reticular changes. Some interstitial pneumonias may exhibit a diffuse distribution of nodules (e.g., sarcoidosis) that appear perilymphatic rather than centrilobular. Scans of diffuse panbronchiolitis documented diffuse centrilobular nodules, always with irreversible bronchiectasis. On HRCT, bronchiolitis obliterans with organizing pneumonia appears as patchy cloudy opacity, predominantly under the pleura and the lower lobe.

The histological characteristic of cryptogenic organizing pneumonia is the presence of Masson bodies within alveolar ducts, alveoli, and bronchioles. It was previously reported that loxoprofen could cause interstitial lung disease and eosinophilic pneumonia (12). This patient continued to take oral loxoprofen even though she had acute lung involvement. In addition, the fraction of eosinophilic granulocytes in blood, pleural effusion, and BALF were all normal. Therefore, we excluded loxoprofen-induced pulmonary toxicity.

Although the pathogenesis of AOSD remains unclear, recent literature supports the hypothesis of innate immunity dysregulation. Abnormalities in cytokine production may have a pathophysiological role. High levels of interleukin (IL) 18 have been observed in the acute phase of AOSD (13), and this cytokine is considered an initiating factor for the inflammatory cascade that includes interferon, IL6, and tumor necrosis factor; the overproduction of these cytokines may account for the symptoms of AOSD. Antoniou et al. (14) reported a case of an eosinophilic pleural effusion in patients with AOSD and observed marked NLRP3 (NRL family, pyrin domain containing 3) inflammasome activation with increased production of IL-1β. This coincided with the development of pleural effusion, which resolved when the patient entered remission.
Pleuritis, interstitial pneumonia, and elevated ferritin levels were demonstrated to be unfavorable prognostic factors for Chinese patients with AOSD (15). Most AOSD patients are treated with corticosteroids in the course of their disease, with an efficacy up to 95%. The present patient was treated with high-dose methylprednisolone, which resulted in remarkable clinical improvement. Her radiological signs of pulmonary involvement showed dramatic changes over a short period.

We conclude that pulmonary involvement in the form of radiologically observed diffuse pulmonary nodules and bilateral pleural effusion is rare in AOSD, but it responds dramatically to glucocorticoid treatment. Regrettably, we did not perform a lung biopsy, so there was no definitive direct evidence of lung injury. It is necessary for clinicians to exclude infections [e.g., bacterial (especially TB), viral, or fungal infection], malignant carcinoma (especially alveolar carcinoma, lymphoma, and leukemia), sarcoidosis, and allergic factors prior to administering high-dose corticosteroids.

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

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**References**