ADULT-ONSET STILL'S DISEASE MISDIAGNOSED AS PNEUMONIA: TWO CASE REPORTS

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Abstract

Adult-onset Still's disease (AOSD) is an uncommon inflammatory condition of unknown origin and pathogenesis. Pulmonary involvement is rare and includes pleuritis and transient radiological infiltrations. We report two cases of AOSD characterized by lung involvement at presentation. Both were misdiagnosed as pneumonia with para-pneumonic effusion. We also discuss the difficulties in diagnosis of AOSD with pulmonary infiltration.

Keywords: Adult-onset Still's Disease; Pneumonia; Misdiagnosis.

Introduction

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disorder with no specific histological features and with unknown origin, characterized by high-spiking fever, an evanescent rash, arthritis, and multiorgan involvement[1]. AOSD is an exclusion diagnosis based on clinical signs and laboratory findings[1]. It is common for AOSD patients to have symptoms involving other organs such as liver, kidney, bone marrow and less often the lungs. Pulmonary involvement includes pleuritis, pleural effusion and transient pulmonary infiltrations[2]. We herein report the clinical case of two patients, whose initial complaints were fever, cough, chest pain, pulmonary infiltrations and pleural effusion, who were misdiagnosed as suffering of pneumonia with para-pneumonic effusion.

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Case Report

Case I

In 2007, a 39-year-old woman presented to her doctor with cough, chest pain and fever. These symptoms had existed for 1 week after four days of sore throat. Chest pain existed in her posterior bilateral sides, which was felt during deep inspiration and cough. The patient had productive cough but no rash and weight loss. Laboratory test revealed that blood leukocyte count was 14,710/mm^3 with a differential count of 86.3% neutrophils. The patient had been extensively examined for infectious disease. The patient had no history of smoking and no lymph nodes. Neoplasm and tuberculosis were considered and excluded. Before admitted into our hospital, she had been treated with intravenous cefoperazone-sulbactam (4.5 g/day) for four days without any improvement of her symptoms. The patient presented breathlessness from the exertion and then was hospitalized. Her family history and previous medical history were unremarkable. On physical examination, the patient's temperature was 39.1ºC, and her heart rate was 116 bpm; blood pressure, 90/60 mmHg; respiratory frequency, 18 breaths/min. Physical examination found dullness on percussion over lung bases and absent breath sounds. The rest of the physical examination was unremarkable.

Laboratory studies were notable and the results were summarized in Table I. Renal function test and D-Dimer were normal. Urine analysis, tuberculin skin test, HIV serology and tumor markers were all negative. Three hemocultures were negative for microorganisms. Antinuclear antigen (ANA), rheumatic factor (RF), antistreptolysin O (ASO) and anti-neutrophil cytoplasmic antibody (ANCA) were negative as well. Bone marrow examination showed inflammatory changes. Serologic tests for Influenza virus A and B, Parainfluenza virus of type 1, 2 and 3, Respiratory syncytial virus, Epstein-Barr virus, Cytomegalovirus, *Klebsiella pneu-*

Table I. Routine laboratory findings for Case 1

	Pre-treatment	Post-treatment	Normal values
ESR (mm/hr)	89	60	Female: 0-20 Male: 0-15
CRP (mg/L)	192	18.9	0-8
Hemoglobin (g/dL)	8.8	11.3	12-17
Leukocyte (/mm3)	15,900	9,040	3,800-10,000
Neutrophils (%)	84.8	74.5	40-72
Platelets (/mm3)	299,000	178,000	100,000-320,000
ALT (IU/L)	62.3	14.2	0-40
AST (IU/L)	42.0	19.5	0-40
LDH (IU/L)	421.6	106	109-245
Serum ferritin (ng/mL)	13,146.58	613.7	Female: <322 Male: <219

ESR: erythrocyte sedimentation rate; CRP: C reactive protein; ALT: alanine aminotransferase; AST: asparate aminotransferase; LDH: lactate dehydrogenase

moniae, Mycoplasma pneumoniae and *Legionella pneumophila* were negative. An abdominopelvic ultrasonograph and echocardiogram showed normal results. ECG showed sinus tachycardia. Chest X-ray showed pleural effusion in bilateral side (Figure 1). Pleural fluid was an exudate, with pleural fluid/serum protein, 0.61; pleural fluid/serum LDH, 0.59; pleural fluid LDH, 248 IU/L. Bacteriological pleural fluid culture was also negative. After pleural effusion was aspirated, a computed tomography (CT) scan of chest showed bilateral lower lobe infiltration (Figure 2). The patient was first diagnosed as pneumonia with a para-pneumonic effusion, and intravenous imipenem and cilastain sodium (3 g/day) and fusidic acid (1.5 g/day) were administered. Three days later, the patient presented with arthralgia in her knees, wrists and elbows.

Seven days later, the patient had no improvement in her symptoms and signs. According to Yamaguchi criteria[3], the patient was finally diagnosed as AOSD, and methylprednisolone (1 mg/kg body weight, 40 mg/day) was initiated. Her symptoms improved markedly in 5 days. Chest CT scan showed normal assessment in 6 days (Figure 3). Laboratory examinations after fourteen days of treatment were listed in Table I. All laboratory findings including serum ferritin levels were normal after two months of treatment. The dose of methylprednisolone was decreased progressively and

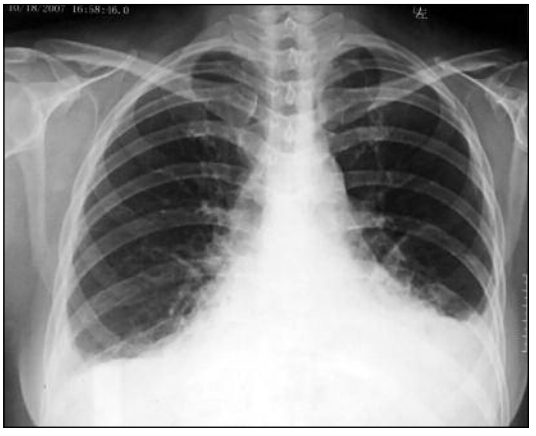

Figure 1. Chest X-ray showing pleural effusion in bilateral side

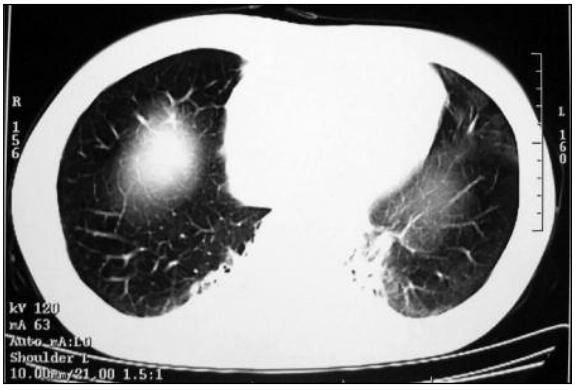

Figure 2. Computed tomography scan of chest showing bilateral lower lobe infiltration after pleural effusion was aspirated

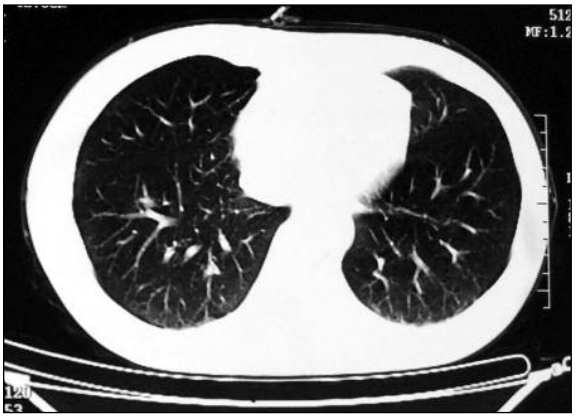

Figure 3. Six days after methylprednisolone treatment, computed tomography scan of chest was normal

withdrawn in six months. The patient's symptoms and signs were stable during the one-year follow--up period. She has fully recovered and no medication is currently prescribed.

Case II

In 2010, a 21-year-old man complained of fever, sore throat, nonproductive cough for 10 days. The spiking fever was over 39ºC. Laboratory findings were summarized in Table II. A chest CT scan showed normal results. He was first diagnosed as sepsis in another hospital and intravenous ceftazidime (4 g/day) and levofloxacin (0.5 g/day) were administered. A week later, there was not any relief of his symptoms and the patient complained of chest pain in his left side, which was felt during inspiration and cough. He was referred to our hospital. His family history and previous medical history were unremarkable. On physical examination, the patient's temperature was 39.2ºC, heart rate was 112 bpm; blood pressure, 120/75 mmHg; respiratory frequency, 21 breaths/min. His pharynx was mildly erythematosus. The remaining physical examination was unremarkable.

The renal function test and D-Dimer were normal. Urine analysis, tuberculin skin test, HIV serology and tumor markers were all negative. Three hemocultures were negative for microorganisms. ANA, RF, ASO and ANCA were negative as well. Bone marrow examination showed inflammatory changes. Serologic tests for Influenza virus A and B, Parainfluenza of type 1, 2 and 3, Respiratory syncytial virus, Epstein-Barr virus, Cytomegalovirus, *Klebsiella pneumoniae*, *Mycoplasma pneumoniae* and *Legionella pneumophila* were negative. An abdominopelvic ultrasonograph and echocardiogram showed normal results. ECG showed sinus tachycardia. The chest CT scan in our hospital showed a left lower lobe infiltration with small pleural effusion in bilateral sides (Figure 4). He was diagnosed as pneumonia with a para-pneumonic effusion, and intravenous imipenem and cilastain sodium (3 g/day) were administered. Two days later, the patient presented a macular rash, concomitant with fever on his trunk and arms, which

Table II. Routine laboratory findings for Case II

	Pre-treatment	Post-treatment	Normal values
ESR (mm/hr)	160	43	Female: 0-20 Male: 0-15
CRP (mg/L)	198.9	67.7	0-8
Hemoglobin (g/dL)	12.8	12.9	12-17
Leukocyte (/mm3)	26,900	17,300	3,800-10,000
Neutrophils (%)	90.1	95.1	40-72
Platelets (/mm3)	413,000	290,000	100,000-320,000
Plasma procalcitonin (mg/L)	0.1	0.22	0-0.1
ALT (IU/L)	76	12	0-40
AST (IU/L)	45	37	0-40
LDH (IU/L)	401	189	109-245
Serum ferritin (ng/mL)	33,159.69	455.45	Female: <322 Male: <219

ESR: erythrocyte sedimentation rate; CRP: C reactive protein; ALT: alanine aminotransferase; AST: asparate aminotransferase; LDH: lactate dehydrogenase

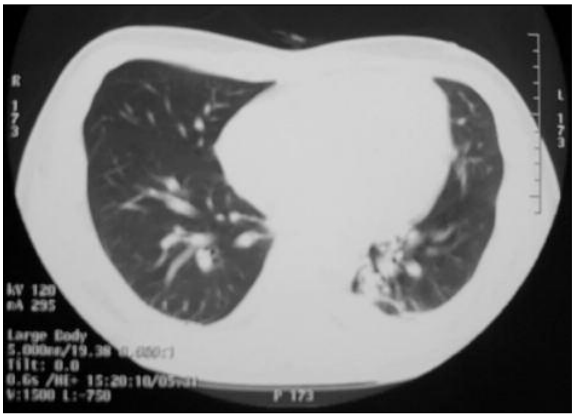

Figure 4. Computed tomography scan of chest showing a left lower lobe infiltration with small pleural effusion in bilateral side

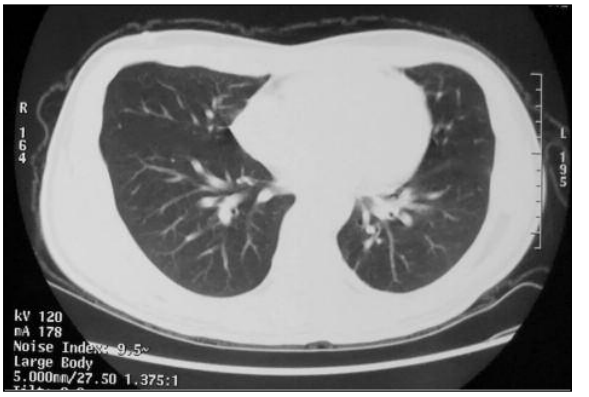

Figure 5. Ten days after methylprednisolone treatment, computed tomography scan of chest was normal

was interpreted as allergic reaction, and antibiotic treatment was changed to intravenous moxifloxacin therapy (400 mg/day) and linezolid (1.2 g/ /day).

Seven days later, the patient had no improvement with medication for pneumonia. According to Yamaguchi criteria[3], the patient was diagnosed as AOSD, and methylprednisolone (80 mg/day) was initiated. His symptoms improved markedly in 1 week. A subsequent chest CT scan showed normal results after ten days of treatment (Figure 5). Laboratory examinations after ten days of treatment were summarized in Table II. Methylprednisolone dose was progressively tapered. The patient has recovered and no medication is currently prescribed.

Discussion

AOSD is a rare condition of unknown etiology usually presenting with high hectic spiking fever accompanied by systemic symptoms[1]. There are no specific laboratory tests for AOSD and the diagnosis is established after exclusion of infections, malignancies and other autoimmune diseases according to the Yamaguchi's criteria[3,4]. Pulmonary involvement in AOSD is rare and even more as first and single AOSD manifestation[2]. Therefore, the association between pulmonary involvement and AOSD is prone to be ignored. The most two common forms of pulmonary involvement are pleural effusion (12-53%) and transient pulmonary infiltrations (6-27%)[2]. Unilateral or bilateral pleuritis or pleurisy (12-53%) with inflammatory pleural fluid has been reported[5]. Interstitial lung disease and fibrosis have been reported with rapid improvement under corticosteroids or nonsteroidal anti-inflammatory drugs[6]. Life-threatening pulmonary complications, such as respiratory distress syndrome and diffuse alveolar hemorrhage, were occasionally reported[7,8]. Spirometry showed a restrictive lung function with low diffusion of CO[9]. Chest X-rays have shown pleural thickening or effusions, pulmonary infiltrations or atelectasis[10,11]. Pulmonary involvement in AOSD seems to be related to pro-inflammtory cytokines, especially IL--18[12].

Our patients first presented with fever, cough, chest pain and lobe infiltration accompanied by pleural effusion. Leukocyte count with a differential count of neutrophils, erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) were found to be markedly elevated in our patients. The patients had been extensively investigated for infectious disease. They were first misdiagnosed as pneumonia with a para-pneumonic effusion. However, the most probable infectious causes were investigated and none was determined. Antimicrobial treatment was unresponsive. Meanwhile, the range of pulmonary infiltration was so small that it might not cause large amount of pleural effusion or even bilateral pleural effusion. Therefore, a noninfectious disease was highly suspected.

The diagnosis of AOSD is difficult in some cases due to the absence of specific serological and pathological findings. The Yamaguchi's criteria are the most widely adopted standards and were shown to be the most sensitive ones (93.5%)[13]. High

levels of serum ferritin seem to be characteristic of AOSD and over 80% of patients present hyperferritinemia[14]. Our patients were diagnosed as AOSD according to the Yamaguchi's criteria[3]. Meanwhile, our patients had extremely elevated serum ferritin level. Therefore, the likelihood of AOSD was high whether other causes, such as infections, malignancies and other autoimmune diseases, were excluded. Moreover, responding to glucocorticosteroid treatment was an important piece of evidence to establish the diagnosis[15].

In conclusion, AOSD is characterized by nonspecific clinical features, which are difficult to be differentiated from many other infectious and noninfectious disorders. When pulmonary infiltration occurs, AOSD is very easily misdiagnosed as pneumonia[16]. Therefore, it is important to consider the diagnosis of AOSD when pulmonary infiltration is involved.

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