Still's Disease Relapse with Severe Pneumonitis after Prolonged Remission

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A 20-year-old woman who had suffered from Still's disease was admitted for fever and progressive pneumonitis after long-term remission. High spiking fever, leukocytosis, splenomegaly and an extremely high serum ferritin concentration strongly suggested a relapse of Still's disease. Intensive therapy with high-dose methylprednisolone, cyclophosphamide and gamma globulin was required for the severe pneumonitis, which was thought to be a rare manifestation in Still's disease.

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Introduction

Pneumonitis, an important manifestation in many systemic rheumatic disorders, greatly influences respiratory function and prognosis. Progressive systemic sclerosis, polymyositis/dermatomyositis, mixed connective tissue disease and rheumatoid arthritis are frequently associated with pneumonitis. In contrast, most of the pulmonary manifestations observed in juvenile onset Still’s disease (JOSD) or adult onset Still’s disease (AOSD) are pleuritis and pleural effusion. Only a few reports have described severe pneumonitis in JOSD/AOSD (1-3). We describe a patient with JOSD exacerbated after prolonged remission in whom rapidly progressive pneumonitis was a prominent feature.

Case Report

The patient was a 20-year-old Japanese woman. She had suffered from juvenile rheumatoid arthritis (JRA) since 1974 (3 y.o.), and during the course of early recurrent spiking fever, typical rheumatoid rash, polyarthralgias, lymphadenopathy, hepatosplenomegaly and pericarditis. On the flare-up at age 13, her symptoms were resistant to steroid; intravenous gamma globulin was given with favorable progress as described previously (4). All symptoms disappeared in 1986 (15 y.o.), and she had remained asymptomatic for 5 years without any medication. However, she became febrile in the beginning of May 1991. Since the antibiotics and diclofenac prescribed by her physician were not effective and daily temperatures of up to 39.5°C accompanied sore throat and progressive dyspnea, she was admitted to our hospital on July 6.

On the day of admission her temperature was 38.2°C in the morning and increased to 39.9°C in the afternoon. Respiration was shallow and rapid, and fine crackles were audible in the lower half of both lung fields. The tonsils were swollen and several cervical lymph nodes ranging from 5 to 10 mm in diameter were palpable. These were discrete and movable. On the left forefinger, an erythematous macule of 10 mm in diameter was observed. There was no finding of arthritis.

The erythrocyte sedimentation rate was 118 mm/h. Hematological examination showed hypochromic microcytic anemia with a hemoglobin level of 9.2 g/dl, hematocrit of 26.4% and red blood cell count of 336x10^6/μl. Thrombocytopenia with a platelet count of 29,000/μl and remarkable leukocytosis with a white blood cell count of 24,200/μl were noted. Serological tests showed elevation of CRP and CH50, while anti-nuclear antibody or rheumatoid factor was not detected. Blood chemistry tests revealed hypoalbuminemia of 2.2 g/dl, glutamic oxaloacetic transaminase of 282 U/l, glutamic pyruvic transaminase of 69 U/l and lactic dehydrogenase (LDH) of 4,959 U/l. Analysis of the LDH isozyme showed predominance of the LDH2 and LDH3 fractions, compatible with pulmonary damage. Creatinine kinase was in the normal range (57 U/l). In addition, the serum ferritin concentration was 23,000 ng/ml, three hundred times the normal upper limit. While detailed respiratory function could not be examined...
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Fig. 1. Roentgenogram of the chest shows a small lung volume and reticular shadows in both lungs that are prominent in the lower lung fields.

Fig. 2. CT scan of the thorax demonstrates diffuse reticular shadows throughout both lungs. Honeycombing is visible in the subpleural area of the right lung.

because of her poor condition, arterial blood gas analysis under supplementary oxygen at a rate of 2 l/min through nasal prongs showed PaO₂ 67 torr and PaCO₂ 35.7 torr. Repeated bacteriological examinations showed no growth of organisms in cultures of blood, urine or sputum. Serum IgM antibody to cytomegalovirus was not detectable and antibodies to other organisms were not elevated.

Chest roentgenogram showed elevation of the diaphragm and reticular shadows in both lungs that were prominent in the lower lung fields (Fig. 1). CT scan of the thorax disclosed diffuse reticular shadows throughout both lungs, and honeycombing was visible in the subpleural area of the right lung (Fig. 2). No pericardial effusion was observed on CT scan or echocardiography. Abdominal ultrasound imaging revealed splenomegaly in 126 mm length. Roentgenogram of the hands demonstrated limited intercarpal ankylosis (Fig. 3).

Taken together, the high spiking fever with afternoon exacerbation, lymph node swelling, splenomegaly, negative findings suggestive of infection, marked elevation of the serum ferritin concentration and radiological findings yielded a diagnosis of relapsed JOSD associated with interstitial pneumonitis. For the progressive respiratory failure, intensive therapy with 1,000 mg/day of methylprednisolone was started from the first hospital day, and continued for 5 days. On day 4, reticular shadows on the chest roentgenogram were increased and PaO₂ was 63 torr under 3 l/min of oxygen supply. Based on these findings, the high-dose methylprednisolone was continued, supplemented with 1,000 mg of intravenous cyclophosphamide on day 4, and 5,000 mg of intravenous gamma globulin from day 4 to 6 (Fig. 4). From the second hospital week, the findings on chest roentgenograms gradually improved, and by day 20 oxygen inhalation was no longer needed. Respiratory function tests on the 65th hospital day showed PaO₂ 91 torr, PaCO₂ 43 torr, %VC 49.5 and %DLCO 25.1. Since her spiking fever persisted in spite of the oral administration of prednisolone, she was given a second gamma globulin therapy on days 55 to 58, and nonsteroidal antiinflammatory drugs (NSAIDs) from day 67.

Discussion

JRA is a distinct clinical entity which apparently differs from adult rheumatoid arthritis in several of its characteristics (5, 6). The American College of Rheumatology criteria for the diagnosis of JRA divide it into three subsets depending on the mode of onset (7). The term “Still’s disease” refers to the subset characterized by prominent systemic manifestations. Since Bywaters (8) described adult patients developing a disease indistinguishable from juvenile onset Still’s disease, the entity “adult onset Still’s disease” has been widely adopted for patients who develop the disease at age 16 or older, resulting in
some confusion in nomenclature. Another term, “adult Still’s disease,” can be used to describe both AOSD and JOSD which has relapsed in adulthood. Although it is still controversial, both JOSD and AOSD share common physical and laboratory features (9), and they may be essentially the same disorder.

The patient described here had repeatedly experienced recurrences of spiking fever of unknown origin, typical rheumatoid rash, polyarthralgias, lymphadenopathy, hepatosplenomegaly and pericarditis until the age of 15 years. She did well without any medication over the subsequent 5 years, but became febrile at 20 years of age. In a review of the long-term history of 21 AOSD patients by Cush et al (10), 4 had had a history of an unexplained acute febrile illness during childhood which may have been an episode of JOSD. Another patient had 8 distinct episodes of systemic involvement with 2 disease-free intervals of 10 years. Thus JOSD/AOSD can relapse even after long-term disease-free intervals.

Although roentgenogram showed bilateral ankylosis of intercarpal joints that is one of the characteristic features of JOSD/AOSD, she did not show clinical signs of arthritis during the current exacerbation. This is not necessarily unique because the number of joints with active arthritis tends to diminish in the long-term course of AOSD (8). We do not know the clinical significance of the erythematous macule observed on admission. The rash was an erythematous, non-itchy macule of 10 mm in diameter on the left forefinger, which was different from the typical JRA rash. However, in spite of the lack of arthritis or typical rash, the fever (≥39°C), negative anti-nuclear antibodies, negative rheumatoid factor, leukocytosis and splenomegaly were compatible with the criteria for AOSD by Cush et al (10). Moreover, she showed a remarkably elevated serum ferritin concentration of 23,000 ng/ml (normal range, 4–70 ng/ml). Ohta et al (11) observed hyperferritinemia in 28 of 34 cases with AOSD, 22 of which had levels 5 times the normal upper limit or higher. Hyperferritinemia is reported to be common in children with JOSD as well (12). Ferritin is one of the proteins produced in acute phase inflammatory response, but patients with rheumatic diseases other than JOSD/AOSD seldom have a serum ferritin level over 4,000 ng/ml (13). This supports our diagnosis of a relapse of JOSD.

The most notable finding in the present case was rapidly progressive respiratory failure. JOSD/AOSD occasionally have respiratory manifestations, but pleuritis and pleural effusions are more common than pneumonitis. Among 21 cases of AOSD reported by Cush et al (10), 9 had pleuritis while pneumonitis was seen in 2 cases. Pneumonitis seems to be less frequent in JOSD. There have been only a few reports of JOSD/AOSD with the severe pulmonary manifestations observed in our case (1–3). Corbett et al (1) described a case of AOSD with severe restrictive pulmonary defect in which the vital capacity was 26.5% of the predicted value, and transbronchial lung biopsy revealed patchy interstitial fibrosis and inflammation. PaO₂ decreased only after exertion. The present case had severe respiratory dysfunction with hypoxemia, and intensive therapy with high-dose methylprednisolone, cyclophosphamide and gamma globulin was needed.

Silverman et al (14) performed a pilot study on the effect of intravenous gamma globulin in JOSD resistant to NSAIDs,
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They observed significant improvement in arthritis in 5 of 8 patients, and extraarticular features in 7 of 8 patients. The present patient also has a history of gamma globulin therapy which successfully induced long-term remission (4). Although we should be cautious to apply this therapy to JOSD/AOSD because of the lack of controlled data to confirm the effectiveness, potential anaphylactic reactions and high cost, the present case was given high-dose gamma globulin 2 times during the current flare-up for the life threatening severe pneumonitis unresponsive to high-dose steroid. Gamma globulin treatments were followed by improvement of pneumonitis and pyrexia, however, combination with steroid and cyclophosphamide made it difficult to evaluate the effect of each therapy precisely. Furthermore, after the second gamma globulin therapy, NSAIDs might contribute to the alleviation of the sustained fever. Even under the treatment with steroid and gamma globulin, combination with NSAIDs may exert an additional effect because the mechanisms of anti-inflammatory actions are not the same among these treatments. Thrombocytopenia seems to be a very rare finding in JOSD/AOSD, which usually show leukocytosis and thrombocytosis. In the literature, one patient with AOSD who had remarkable leukocytosis associated with thrombocytopenia and hemolytic anemia is described, but the details are not included (15). Two other cases of cytopenia with JOSD/AOSD are reported: one was a juvenile case with a WBC of 2,600/µl and platelet count of 117,000/µl; the other was an adult case with a WBC of 3,200/µl and platelet count of 51,700/µl (16). They do not seem to have been given medication before the cytopenia was noticed. The cause of the cytopenia was not clear. Because the latter case responded to splenectomy, the authors considered that hypersplenism caused the cytopenia in that case. Immune mechanisms responsible for the cytopenia in JOSD/AOSD have not been proposed to date. In the present patient, thrombocytopenia had not been noticed until she suffered from pneumonitis, and the effect of antibiotics and an antiinflammatory drug, given by her physician, on thrombocytopenia cannot be excluded, however, it should be noted that leukopenia and thrombocytopenia can be encountered in the course of JOSD/AOSD.

References