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Juvenile idiopathic arthritis with pulmonary hemosiderosis: a case report

Szu-Hung Chu, Shyh-Dar Shyur, Ya-Hsuan Peng, Cheng-Yu Wu, Ching-Long Chang, Chung-Lin Lai, Wen-Chiu Wu

Department of Pediatrics, Mackay Memorial Hospital, Taipei, Taiwan, ROC

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Pleuropulmonary disease is occasionally seen in association with juvenile idiopathic arthritis. There have been few case reports of pulmonary hemosiderosis associated with juvenile idiopathic arthritis. We describe a case of a 3-year-old girl with iron deficiency anemia, juvenile idiopathic arthritis, and pulmonary hemosiderosis. Arthralgia of the left knee was noted 2 weeks after the diagnosis of iron deficiency anemia, and juvenile idiopathic arthritis was diagnosed 9 months later. She was treated with naproxen and prednisolone. Her joint symptoms were well controlled after the treatment. Six months later, hemoptysis developed and pulmonary hemosiderosis was diagnosed. She was again treated with naproxen and prednisolone and no more pulmonary or joint symptoms developed during more than 1-year follow-up.

Key words: Juvenile idiopathic arthritis, juvenile rheumatoid arthritis, pulmonary hemosiderosis

Pleuropulmonary involvement in juvenile idiopathic arthritis (JIA) occurs in only 4% of patients, and pleural involvement is more common than involvement of the lung parenchyma [1]. Hemosiderin-laden macrophages in the alveoli, iron deficiency anemia (IDA), and roentgenographic abnormalities of the lung characterize pulmonary hemosiderosis [2]. Pulmonary hemosiderosis may be primary or secondary. Idiopathic pulmonary hemosiderosis and Goodpasture's syndrome are 2 kinds of primary pulmonary hemosiderosis. The secondary form of pulmonary hemosiderosis usually occurs in association with cardiac or rheumatic diseases. Heiner *et al* [3,4] listed the following conditions associated with pulmonary hemosiderosis: polyarteritis nodosa, Wegener's granulomatosus, systemic lupus erythematosus, rheumatic fever, rheumatoid arthritis, and Henoch-Schonlein purpura. We report the case of a 3-year-old girl with JIA and pulmonary hemosiderosis.

Case Report

A 3-year-old girl was admitted to pediatric ward of the Mackey Memorial Hospital due to cough, rhinorrhea, and low-grade fever for 1 week. Physical examination revealed pale conjunctiva and mildly coarse breathing sounds. Laboratory data revealed hemoglobin of 5.7 gm/dL, hematocrit of 21.2%, red blood cell count of 2.92 million, mean cell volume of 72, and reticulocyte count of 2.5%. Peripheral blood smear was consistent with hypochromic microcytic anemia. The serum iron was 32 μg/dL (normal range, 44-164 μg/dL). The ferritin and transferrin levels were 147 ng/mL and 297 ng/mL (normal range, 200-360 ng/mL), respectively. The total iron binding capacity was 340 μg/dL (normal range, 260-445 μg/dL). Direct and indirect Coombs' tests were negative and hemoglobin electrophoresis was normal. The *Mycoplasma* profiles were negative. Chest X-ray was compatible with viral pneumonitis. These findings led to a diagnosis of viral pneumonia and IDA. She was given a blood transfusion, iron supply therapy, and supportive care. Two weeks later, she experienced severe pain and reddish swelling of her left knee. X-ray of the left knee was normal. Her knee joint pain was intermittent, and painful swelling of her right ankle and the second proximal interpharyngeal joint of her left hand developed later. Nine months after the initial diagnosis of viral pneumonia and IDA, JIA was diagnosed, and she was treated with naproxen and prednisolone. Immunoglobulin and complement were normal. B cells, T cells, and NK cells were normal, and HLA-B27 was negative. Rheumatoid factor was 2460 IU/mL (normal, <20 IU/mL) and antinuclear factor was 40 with a speckled pattern. The erythrocyte sedimentation rate was 57 mm/h. She responded very well to treatment. Severe cough with bloody sputum and low-grade fever developed 6 months later.

Corresponding author: Dr. Shyh-Dar Shyur, Department of Pediatrics, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, 104, Taiwan, ROC. E-mail: abc 1016@ms2.mmh.org.tw

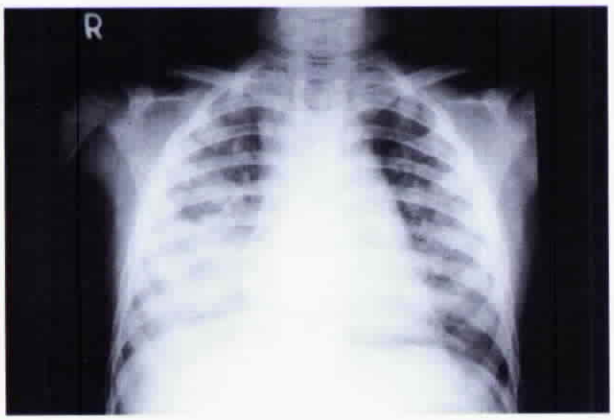

Fig. 1. Chest film revealed bilateral reticulonodular infiltrates.

Laboratory investigations revealed a hemoglobin of 10.4 gm/dL, a hematocrit of 34.1%, and a mean cell volume of 71.9. Serum ferritin was 67.2 ng/mL and the erythrocyte sedimentation rate was 69 mm/h. Chest X-ray revealed bilateral reticulonodular infiltrates (Fig. 1). Iron stain of the sputum revealed numerous hemosiderin-laden macrophages, compatible with pulmonary hemosiderosis (Fig. 2). Her pulmonary symptoms disappeared gradually after the reinstitution of daily steroid therapy (2 mg/kg/d prednisolone). Her joint symptoms also improved gradually. There was no recurrence of pulmonary hemosiderosis or arthritis for more than 1 year. Follow-up laboratory data revealed a rheumatoid factor of 607 IU/mL and complement was normal.

Discussion

Pleuropulmonary manifestations of JIA in children are occasionally reported [5]. In 1980, Athereya *et al* [1] described the pulmonary manifestations of juvenile rheumatoid arthritis (JRA), including pleurisy with or without effusion, transient pneumonitis, diffuse interstitial disease, lymphoid bronchiolitis, amyloidosis, pulmonary arteritis, and idiopathic pulmonary hemosiderosis. The relationship between pulmonary hemosiderosis and JIA was described by Cunnigham and Hammond [6] in 1961. They reported a 5-year-old girl with JRA who experienced pulmonary hemosiderosis 2 years after JRA was diagnosed. In a 1962 report, Lemley and Katz [7] suggested that pulmonary hemosiderosis was not idiopathic, but rather a presenting manifestation of rheumatoid arthritis. In 1966, Smith [8] reported a child who experienced pulmonary hemosiderosis at 1 year of age, which persisted to the age of 10 years. Seropositive rheumatoid arthritis developed when she was 13 years old. In 1980, Athereya *et al* [1] reviewed 8 cases of JRA with pleuropulmonary disease and found that only one girl with systemic JRA had pulmonary hemosiderosis 18 months after the diagnosis of JRA was given. In 2000, Topaloglu *et al* [9] reported a Turkish boy with seronegative polyarticular JRA who experienced pulmonary hemosiderosis 2 months after the onset of JRA. Pulmonary hemosiderosis can develop before or during the coarse of JIA. This patient first presented with IDA and viral pneumonia. We suspected that she had pulmonary hemosiderosis at that time. Two weeks later, symptoms of arthritis started. Pulmonary hemosiderosis was diagnosed 15 months after the onset of arthritis.

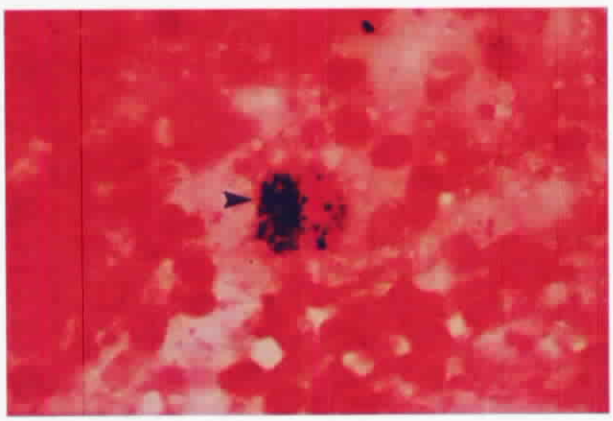

Fig. 2. Sputum smear with Prussian blue staining for hemosiderin showed hemosiderin accumulating in the macrophage (arrow head). (1000x)

In pulmonary hemosiderosis, there is persistent or chronic bleeding in the alveoli, and macrophages convert the iron of hemoglobin into hemosiderin [10]. Heart disease such as mitral stenosis can lead to intrapulmonary hemorrhage due to an increase in the pulmonary venous pressure. An immune process can also destroy the pulmonary vasculature. Immune complex deposition or formation can be demonstrated in systemic lupus erythematosus and Goodpasture's syndrome [11,12]. But in cases of pulmonary hemosiderosis associated with JRA, there is no specific antigen-antibody reaction to the basement membrane [13]. In 2 biopsies where immunofluorescent staining was done, there was no evidence of immunoglobulin deposition [1]. On the other hand, pulmonary hemosiderosis is associated with a variety of collagen vascular diseases and it has been successfully treated with corticosteroids. This patient developed pulmonary hemosiderosis, which may be a consequence of the inflammatory process, but its pathophysiology is not fully understood [14].

The usual clinical features of pulmonary hemosiderosis include fever, tachypnea, leukocytosis, and

respiratory distress [2]. Symptoms of severe cough and hemoptysis, dyspnea, and pallor can be seen in these patients. The anemia is microcytic and hypochromic. The reticulocyte count may be elevated and the serum iron concentration is low. Cough, hemoptysis, and IDA were present in the patient in this report. The chest X-ray changes of pulmonary hemosiderosis range from minimal infiltrates to massive pulmonary involvement with secondary atelectasis. In this patient, chest X-ray revealed reticulonodular infiltrates when she had a severe cough with bloody sputum. These infiltrates decreased after steroid treatment.

The diagnosis of pulmonary hemosiderosis is made by combining particular clinical findings (hemoptysis, cough, and dyspnea) and specific roentgenographic and laboratory findings (reticulonodular infiltration on chest X-ray and IDA) together with sputum, bronchoalveolar fluids, or lung biopsy specimens showing hemosiderin-laden macrophages. In this patient, hemosiderin-laden macrophages were present in the sputum. This confirmed the presence of alveolar hemorrhage and the diagnosis of pulmonary hemosiderosis.

New classification criteria for JIA were established in 1997 [15]. There are 7 types of JIA in this classification including systemic arthritis, oligoarthritis, rheumatoid factor negative polyarthritis, rheumatoid factor positive polyarthritis, psoriatic arthritis, enthesitis related arthritis, and "other" arthritis (fits no other category or fits more than one category). In oligoarthritis JIA, the rheumatoid factor must be negative. Because the rheumatoid factor was positive and only 3 joints were involved in this patient, this case did not fit the oligoarthritis type or the rheumatoid factor positive polyarthritis category. The patient's condition fell into the "other" category. Though pleuropulmonary disease is seen commonly in association with systemic JIA, it can also occur in the pauciarticular and polyarticular types [16]. In adult rheumatoid arthritis, rheumatoid factor may have a role in enhancing the pathogenicity of immune complex mediated injury to the lung [17]. In some JIA patients with pleuropulmonary involvement, rheumatoid factor is found in the serum, but the role of this rheumatoid factor in the lung is still unclear [1,7,8].

Patients with JIA and pulmonary hemosiderosis respond to high-dose steroids [1,8,9,18]. After treatment, the chest X-ray and pulmonary function can become normal and the hemoglobin level can improve. Patients with JIA and pulmonary hemosiderosis usually recover fully. Some of them have residual abnormalities such as roentgenographic evidence of interstitial fibrosis, and minimal abnormalities of pulmonary function [1]. The patient in this study was treated with prednisolone 2 mg/kg/d, and her symptoms gradually subsided. During more than a year of follow-up, there was no recurrence of her pulmonary hemosiderosis and her arthritis was well controlled.

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