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Methotrexate pneumonitis in a patient with rheumatoid arthritis

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Methotrexate pneumonitis is an unpredictable and life-threatening side effect of methotrexate therapy. Early diagnosis, cessation of methotrexate, and treatment with corticosteroids and/or cyclophosphamide are important in the management of patients with methotrexate pneumonitis. Methotrexate pneumonitis has not been reported in patients of Chinese ethnicity. We report a case of methotrexate pneumonitis in a Taiwan patient with rheumatoid arthritis who presented with acute nonproductive cough, dyspnea, fever, severe hypoxemia, and rapid progression to respiratory failure. Chest roentgenogram demonstrated bilateral diffuse interstitial and alveolar infiltration. Thoracoscopic biopsy with wedge resection of the upper lobe of the right lung was performed and the histologic findings of the biopsy specimen were consistent with bronchiolitis obliterans with organizing pneumonia. Rapid improvement of methotrexate pneumonitis was achieved after pulse therapies of methylprednisolone and cyclophosphamide and daily use of prednisolone.

Key words: Methotrexate pneumonitis, rheumatoid arthritis

Methotrexate (MTX), a folic acid antagonist, was first introduced to treat patients with psoriasis, psoriatic arthritis, and rheumatoid arthritis in 1951 [1]. Low-dose, weekly-pulse MTX has become a widely used and effective treatment for patients with rheumatoid arthritis [2]. Methotrexate pneumonitis, an adverse effect of MTX, is unpredictable and may become life-threatening. Methotrexate pneumonitis was first reported in 1969 [3]. A prevalence of 5.5% and an incidence of 3.9 cases per 100 patient-years of MTX exposure have been reported [4]. More than 120 cases have been reported [5]. However, our review of the literature found no reports of MTX pneumonitis in patients of Chinese ethnicity in Medline (1966-2001), the Chinese Traditional Medicine Database (China), Chinese Dissertation Reference Compact Disc (China), Chinabase-Medicine (China), Chinese-English Journal United Index Database (China), and Index to Chinese Periodical Literature (Taiwan). We report here a case of MTX pneumonitis in a Taiwan patient with rheumatoid arthritis, who was successfully treated with discontinuation of MTX use, pulse therapies of methylprednisolone and cyclophosphamide, and then daily use of prednisolone.

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Case Report

A 55-year-old woman experienced seropositive chronic additive symmetric polyarthritis since 1991. She visited Taichung Veterans General Hospital in February 1993. Roentgenograms of both hands and feet disclosed joint space narrowing and marginal erosion over bilateral radiocarpal and carpal joints, intertarsal joints, and metatarsophalangeal joints. In March 1993, salazopyrin 1500 mg/d, gold sodium thiomalate 50 mg intramuscularly weekly, sulindac 400 mg/d, and prednisolone 7.5 mg/d were administered. Chest roentgenograms showed interstitial infiltration over both lung fields in December 1996. Methotrexate (7.5 mg/week) was added in June 1997. She was enrolled into a phase III double-blind trial of Etanercept (enbrel) with concomitant use of MTX (15 mg/week), prednisolone (7.5 mg/d), and sulindac (400 mg/d) in October 2000. Nonproductive cough, shortness of breath, and fever developed on December 27, 2000. She was admitted to intensive care unit due to severe dyspnea on January 17, 2001. Physical examination revealed acute appearance, clear consciousness, and severe respiratory distress. Vital signs were as follows: blood pressure 112/68 mm Hg; pulse rate 103/min; respiratory rate 30/min; and body temperature 39°C. Chest auscultation found crackles

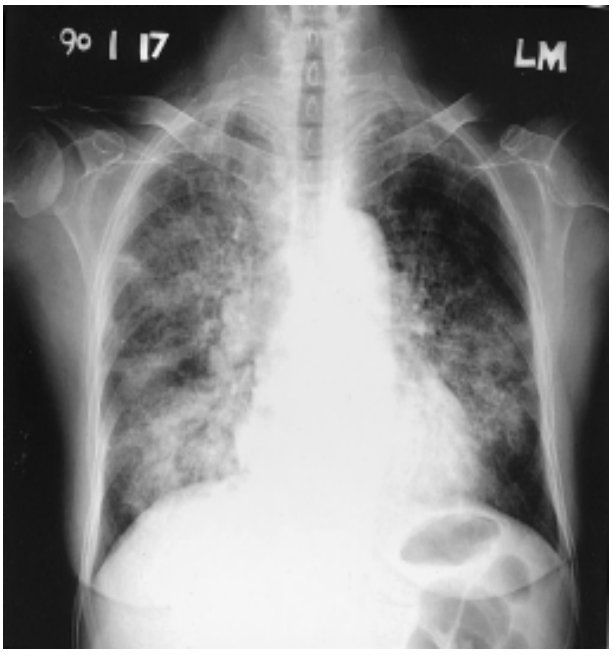

Fig. 1. Bilateral mixed interstitial and alveolar infiltration in the patient's lungs on admission to the intensive care unit.

in both lung fields. The physical findings from the heart and abdomen were normal. Chest roentgenogram (Fig. 1) revealed bilateral diffuse interstitial and alveolar infiltration. Arterial blood gas analysis on room air disclosed pH 7.373; pCO_2 37.7 mm Hg; pO_2 57 mm Hg; HCO_3^- 22.1 mEq/L; and O_2 saturation 88.5%. Other laboratory findings included white blood cell count (WBC) 13 800 /mm^3 with neutrophils at 89.7%, lymphocytes at 6.3%, monocytes at 3.9%, eosinophils at 0.1%; red blood cell count 3.58 M /mm^3; platelet count 552 000 /mm^3; albumin 2.9 g/dL; creatinine 0.9 mg/dL; and C-reactive protein 20 mg/dL (normal range, <0.8 mg/dL). Urinalysis results were normal. Serologic test results, including *Chlamydia* immunoglobulin M antibody, *Legionella* indirect fluorescent antibody, and *Mycoplasma pneumoniae* immunoglobulin M antibody were negative. All the results of bacterial or fungal stains and cultures of blood, sputum, and urine were negative. Fiberoptic bronchoscopy performed on January 19, 2001 revealed no abnormalities. The cell count from bronchoalveolar lavage (BAL) was 75 x 10^3/mL with histiocytes at 87%, lymphocytes at 2%, neutrophils at 10%, and eosinophils at 1%. Culture of the BAL fluid was negative for virus and bacteria. The patient received endotracheal intubation and mechanical ventilation support due to acute respiratory failure on the 1st day after admission. Broad-spectrum antibiotics were prescribed initially. Methotrexate and etanercept were discontinued. Information provided from the clinical trial showed that she was in the placebo group. Her lung condition did not improve. Thoracoscopic biopsy with wedge resection of the upper lobe of the right lung was performed on the 14th day after admission. The histopathologic findings of the lung biopsy were consistent with bronchiolitis obliterans with organizing pneumonia (BOOP) (Fig. 2). Pathologic findings including interstitial inflammation and fibrosis, type II pneumocyte hyperplasia, and increased intraalveolar macrophage were also noted. No *Pneumocystis carinii* was found. Under the impression of MTX pneumonitis, pulse therapy of methylprednisolone (750 mg for 3 consecutive days from the 15th hospital day) and cyclophosphamide pulse therapy (300 mg on the 19th hospital day) were given. The clinical symptoms and the abnormalities on the chest roentgenograms were much improved. Mechanical ventilation was discontinued 4 days after the end of methylprednisolone pulse therapy. She was discharged with a prescription of 25 mg/d oral prednisolone on February 17, 2001. Another 5 courses of monthly cyclophosphamide pulse therapy were given and further improvement of the chest symptoms and the abnormalities on the chest roentgenograms were noted 6 months after discharge.

Discussion

Methotrexate pneumonitis is uncommon in patients with rheumatoid arthritis. The clinical features in this patient included fever, nonproductive cough, dyspnea, tachypnea, mild leukocytosis (WBC <15 000 /mm^3), diffuse interstitial and alveolar infiltrates on chest roentgenogram, pathologic findings of BOOP in open-lung biopsy, and negative microorganism culture

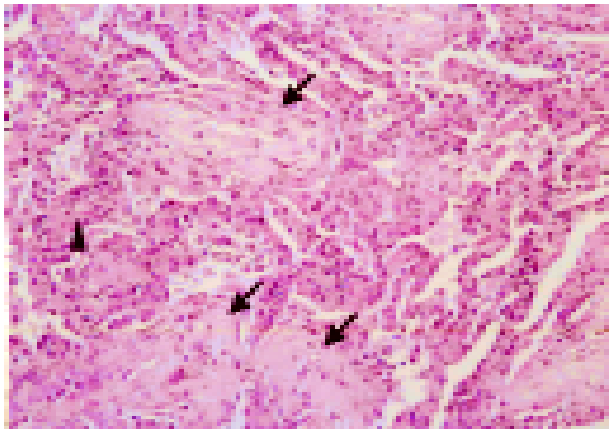

Fig. 2. Plugs of young fibrous tissue in the lumens of terminal bronchioles and alveolar dusts (arrow) and interstitial inflammatory cell infiltration (arrowhead) in the open lung biopsy (H-E stain, 200x).

including *P. carinii* in the lung. These features fulfilled the diagnostic criteria of MTX pneumonitis proposed by Kremer [6]. The sensitivity of these proposed criteria, which have been used in clinical studies, have not been studied. A patient with viral pneumonitis may also fulfill these criteria [7]. However, viral pneumonitis is a self-limited disease. A correlation between clinical and radiographic improvement within 2 to 3 weeks has been observed in survivors [8]. This patient did not show any improvement during the first 2 weeks of hospitalization until a large dose of methylprednisolone was administered. The clinical course was thus not compatible with viral pneumonitis.

The duration of MTX therapy, the total cumulative MTX dose, and the weekly dose at the time of onset of MTX pneumonitis in this patient were 186 weeks, 1685 mg, and 15 mg/week, respectively. Kremer *et al* [6] reported the mean duration of MTX therapy in a series of 29 patients was 66.1 ± 91 weeks (range, 1-480 weeks; median, 61 weeks), the total cumulative MTX dose was 540 ± 758.5 mg (range, 7.5-3600 mg; median, 270 mg), and the mean weekly dose was 9.7 ± 3.4 mg (range, 5-22.5 mg; median, 7.5 mg) at the onset of MTX pneumonitis. The risk factors did not seem to be related to the cumulative dose, duration, or weekly dose of MTX.

In a case-control study, Alarcon *et al* [9] found that the strongest predictors of MTX lung injury were older age, diabetes, rheumatoid pleuropulmonary involvement, previous use of disease-modifying anti-rheumatic drugs (DMARDs), and hypoalbuminemia. Among these factors, previous use of DMARDs and hypoalbuminemia had the highest attributable risks. The risk factors for MTX pneumonitis in this patient included previous use of DMARDs, hypoalbuminemia, and preexisting interstitial lung disease.

The mechanisms of MTX pneumonitis remain unclear. Hypersensitivity reaction or direct toxic effect of MTX has been proposed as a possible cause [10]. Hypersensitivity reaction was supported by the pathologic findings of interstitial pneumonitis, granuloma formation, bronchiolitis, peripheral eosinophilia, and responsiveness to corticosteroids. Findings of BAL were nonspecific and could not confirm the diagnosis of MTX pneumonitis. However, BAL studies may be useful to detect the presence of infectious process [11] and differentiate between MTX pneumonitis and interstitial lung disease in patients with rheumatoid arthritis [12]. Methotrexate pneumonitis may be associated with lymphocytic alveolitis, in which an increase in the lymphocytes can be found in the BAL fluid [12]. A disproportionate increase in $CD4^+$ cells and in the CD4/CD8 ratio in the BAL fluid may be observed and differ from that in interstitial lung disease due to rheumatoid arthritis [12]. Bronchiolitis obliterans with organizing pneumonia was the main pathologic finding in this patient. Other pathologic findings including interstitial inflammation and fibrosis, type II pneumocyte hyperplasia, and increased intraalveolar macrophage were nonspecific but frequently seen in MTX pneumonitis [5]. Bronchoalveolar lavage findings from this patient were nonspecific and showed no lymphocytosis. Bronchiolitis obliterans with organizing pneumonia is a nonspecific histopathologic pattern of lung injury that can be a manifestation of pulmonary drug injury, such as MTX pneumonitis [13], and may occur in 8.2% of patients with MTX pneumonitis [5]. Bronchiolitis obliterans with organizing pneumonia may also be one of the pulmonary manifestations of rheumatoid arthritis. The clinical features of BOOP in rheumatoid arthritis are nonspecific and may develop subacutely over weeks to months [14]. In this case, the rapid development of respiratory failure was not compatible with BOOP in rheumatoid arthritis.

The majority of patients with MTX pneumonitis recover rapidly after adequate steroid treatment. Patients with steroid-resistant MTX pneumonitis may improve rapidly after intravenous cyclophosphamide pulse therapy [15]. Repeat treatment with MTX may cause recurrence of MTX pneumonitis or death, and is discouraged [6]. In this case, MTX pneumonitis responded well to methylprednisolone and cyclophosphamide pulse therapies.

In conclusion, rapid exclusion of infection, high index of suspicion based on clinical features, pathological finding of lung biopsy, and cessation of MTX use are the keys to diagnosis and successful treatment of MTX pneumonitis. Of these, immediate cessation of MTX treatment is the most important.

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