Weekly Low-Dose Methotrexate Therapy for Sarcoidosis

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Low-dose methotrexate therapy has been used to treat a variety of chronic inflammatory diseases; a few studies have discussed the efficacy of this therapy for sarcoidosis. We present a patient with symptomatic sarcoidosis who was successfully treated with low-dose methotrexate after being refractory to steroids. This patient showed significant clinical improvement without development of any severe side effects. These findings suggest that low-dose methotrexate therapy may be a useful alternative treatment for sarcoidosis.

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Introduction

Methotrexate is a folic acid antagonist that is used as an antimetabolite at high doses to treat malignancy. Recently, low-dose methotrexate therapy has been shown to be effective in the treatment of a variety of chronic inflammatory diseases, such as psoriasis, inflammatory bowel disease, rheumatoid arthritis, and bronchial asthma (1–4). However, there have been few reports on the efficacy of methotrexate for sarcoidosis (5–8). We report herein a patient with steroid-resistant sarcoidosis who was successfully treated with low-dose methotrexate.

Case Report

A 39-year-old man was admitted to our hospital for the evaluation of chest X-ray findings in 1984. The chest X-ray film showed bilateral hilar lymphadenopathy and small nodular infiltrates in the upper lung fields. A diagnosis of sarcoidosis was made on the basis of uveitis, elevated serum angiotensin converting enzyme (SACE) level, and the detection of sarcoid granulomas by transbronchial lung biopsy (TBLB). The lung specimens revealed scattered, well-demarcated, non-caseating epithelioid granulomas with little interstitial fibrosis, involving predominantly the interstitium. Four years later, chest X-ray films showed marked shrinkage of upper lobes due to pulmonary fibrosis and he developed a productive cough. Since 1987, he received 60 mg of prednisolone on alternate days, but the respiratory symptoms progressively worsened and his pulmonary function deteriorated.

In July 1991, he was readmitted for further treatment. On

physical examination, breath sounds were diminished at the bilateral lung apices, but no rales were audible. The heart sounds were normal with no murmurs. Nodular skin lesions with a keloid-like appearance were found on both sides of the knees.

Laboratory findings showed a white blood cell count of 4,500/mm³, an erythrocyte sedimentation rate (ESR) of 45 mm/h, a serum lactic dehydrogenase (LDH) level of 450 WU (normal range: 100–400 WU), and a serum IgG concentration of 2,155 mg/dl (1,300–1,800 mg/dl). The SACE level was 15 IU/l (8.3–21.4 IU/l), and the serum lysosome level was slightly elevated to 14.2 µg/ml (5.0–10.2 µg/ml). There were no abnormalities on the ECG and Holter ECG recordings. The tuberculin skin test revealed a negative reaction. Biopsy of the nodular skin lesions proved them to be non-caseating epithelioid granulomas.

The chest X-ray film demonstrated consolidations and nodular infiltrates which predominantly affected the upper lung fields (Fig. 1A), and high resolution computed tomography (HRCT) showed conglomerated masses and nodules with distortion of the lung parenchyma (Fig. 2A). An increased uptake of ⁶⁷Ga-citrate in the lungs was seen (Fig. 3A). Pulmonary function tests revealed a mild restrictive impairment (FVC, 2.63 L; %FVC, 66.2; FEV1, 2.20 L), and arterial blood gas analysis showed a pH of 7.411, a PCO₂ of 37.2 Torr, and a PO₂ of 78.8 Torr.

In September 1991, he was started on oral methotrexate at 7.5 mg once a week. Clinical improvement was noted after 2–3 weeks. His productive cough gradually subsided and there was a significant improvement in pulmonary function, as assessed by the FVC and arterial blood gases (Fig. 4). Addition-

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Fig. 1. Chest X-ray films. (A) On admission. Note consolidations and nodular infiltrates predominantly in upper lung fields. (B) After 3 months of therapy. Note the marked decrease in consolidations and nodular infiltrates.

ally, there was a decrease of the ESR, serum LDH level, and SACE level. The chest X-ray findings were also markedly improved (Fig. 1B), and the nodules and alveolar consolidation detected by HRCT showed a decrease (Fig. 2B). Furthermore, the lung uptake of Ga-citrate was significantly diminished (Fig. 3B). After treatment, the percentage and number of BAL lymphocytes decreased (Table 1), and the number of CD4+ T lymphocytes and HLA-DR+ lymphocytes also decreased. However, the CD4:CD8 ratio of BAL T lymphocytes showed a marked increase. Even the skin lesions improved slightly. Although he experienced nausea during the first week of therapy, this was resolved in 2–3 weeks without specific treat-

Fig. 2. High resolution computed tomography (HRCT) scans of chest. (A) On admission. Note conglomerated mass and nodules. (B) After 3 months of therapy, the opacities showed a significant decrease.

Fig. 3. ^{67}Ga -citrate scintigraphy. (A) On admission. Note the increased uptake in the lung. (B) After 3 months of therapy, the lung uptake was markedly diminished.

ment. No severe side effects, including hematologic or hepatic toxicity, were observed. After 6 months of therapy, the methotrexate regimen was changed to administration every 2 weeks. However, his condition remained stable and no deterioration occurred until 6 months later.

Discussion

Low-dose methotrexate therapy was first used as a treatment for psoriasis (1) and thereafter was used for several other inflammatory diseases. For example, recent studies have demonstrated the efficacy of low-dose methotrexate for rheumatoid arthritis and bronchial asthma (3, 4). This drug has been found to have a steroid-sparing effect and to cause no serious adverse reactions at low doses.

Despite the increasing use of low-dose methotrexate therapy for a variety of inflammatory diseases, only a few reports have suggested the efficacy of this therapy for sarcoidosis (5–8). Israel reported that patients with progressive sarcoidosis who show steroid resistance or steroid intolerance respond to methotrexate at a dose of 20 mg twice weekly (5). It was also shown that administration of methotrexate at 25 mg weekly led to a significant improvement in cutaneous sarcoidosis (6). More recently, Lower demonstrated that the administration of methotrexate at 10 mg weekly is effective in chronic symptomatic sarcoidosis without severe side effects, and has a steroid-sparing effect (8).

In the present sarcoidosis patient, a significant improvement was seen with weekly low-dose methotrexate treatments. Although his disease was resistant to steroid therapy, it responded well to methotrexate and there were no severe side effects. Clinical improvement was observed within 1 month. Methotrexate is known to cause dose-related adverse side effects, such as pancytopenia, liver damage, and pneumonitis. However, low-dose methotrexate only rarely causes hematologic, hepatic, or pulmonary toxicity (9–11), and the most common problem is gastrointestinal symptoms. Although the present patient complained of nausea during the initial phase of therapy, he soon became tolerant of the drug. Thus, our findings confirm that low-dose methotrexate is useful alternative therapy for patients with sarcoidosis who show resistance or intolerance for steroids.

The mechanism by which low-dose methotrexate acts in sarcoidosis remains unclear. In rheumatoid arthritis, several studies have demonstrated that low-dose methotrexate has an antiinflammatory effect, without an immunosuppressive effect on humoral or cell-mediated immunity (12). Low-dose methotrexate has also been shown to decrease neutrophil chemotaxis in response to C5a and LB4 (13, 14). In addition, it has been found that this therapy decreases hydrogen peroxide and TNF release by alveolar macrophages as well as reducing the number of BAL lymphocytes and the CD4:CD8 ratio of BAL T lymphocytes in sarcoidosis (15). These findings suggest that low-dose methotrexate has a direct effect on macrophages and T lymphocytes at the sites of inflammation.

The present patient treated with low-dose methotrexate also showed a decrease of BAL lymphocytes and CD4+ T lymphocytes after 3 months. However, CD8+ T lymphocytes also decreased markedly, resulting in an increase in the CD4:CD8 ratio. The reason for this increase in the CD4:CD8 ratio of BAL T lymphocytes despite significant clinical improvement, is unclear. Although the CD4:CD8 ratio is generally considered to reflect disease activity in sarcoidosis, some patients have been found to improve despite an increase of this ratio in BAL T lymphocytes, therefore it may not necessarily be correlated with disease activity.

The present findings indicated that low-dose methotrexate therapy is effective for the treatment of sarcoidosis and has low toxicity. However, it is unclear whether or not this therapy can improve the long-term prognosis of sarcoidosis by preventing pulmonary fibrosis and impairment of lung function. Thus,

Fig. 4. Clinical course.

Table 1. Effects of Low-Dose Methotrexate Therapy on BALF Findings

	Before therapy	3 months of therapy
Recovery rate, %	55.5	56.5
Total cell count, 10 ⁴ /ml BALF	7.66	7.96
Differential cell count, % (10 ⁴ /ml BALF)		
Macrophages	77.6 (5.94)	86.3 (6.87)
Lymphocytes	17.5 (1.34)	11.7 (0.93)
Neutrophils	0.3 (0.02)	1.5 (0.12)
Eosinophils	4.6 (0.35)	0.5 (0.04)
Phenotypes of lymphocytes, % (10 ³ /ml BALF)		
CD3	73.3 (9.82)	69.4 (6.45)
CD4	51.8 (6.94)	65.6 (6.10)
CD8	25.3 (3.39)	13.4 (1.25)
HLA-DR	67.8 (9.08)	58.7 (5.46)
CD4/CD8	2.05	4.90

further follow-up studies are needed to assess the long-term efficacy and safety of low-dose methotrexate therapy for sarcoidosis.

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