

Successful Combination Therapy of Cyclosporine and Methotrexate for Refractory Polymyositis with Anti-Jo-1 Antibody : A Case Report

Although corticosteroids have been the initial agent for the treatment of inflammatory myopathies (IM), immunosuppressive agents such as azathioprine, methotrexate, cyclophosphamide, or cyclosporine are commonly required to control the disease except mild cases. On the other hand, the efficacy of combination therapy of cyclosporine and methotrexate in severe rheumatoid arthritis has been proven without serious side effects. However, in treatment-resistant myositis, the experience of such a therapy is very limited, and has not been described in refractory polymyositis with anti-Jo-1 antibody. Here, we report a young female patient with recalcitrant polymyositis and anti-Jo-1 antibody who was successfully treated with the combination therapy of cyclosporine and methotrexate. At first, the myositis did not respond to several agents, such as corticosteroid, monthly pulse cyclophosphamide, azathioprine, or cyclosporine. Methotrexate was initially avoided as treatment regimen because of its potential pulmonary toxicity in the case with preexisting lung disease.

Key Words: Polymyositis; Anti-Jo-1 Antibody; Cyclosporine; Methotrexate

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INTRODUCTION

The inflammatory myopathies (IM) are a heterogeneous group of disorders characterized by chronic inflammation of striated muscles (polymyositis) and sometimes skin (dermatomyositis). Polymyositis can be further divided into several subgroups. Patients with IM of any category may have autoantibodies. Antibodies against aminoacyl-tRNA synthetase (anti-synthetase antibodies) among these autoantibodies are known to be highly specific for IM. Anti-Jo-1 antibody is the most frequently identified antibody of the group of antisynthetases, and is detected more commonly in polymyositis than in dermatomyositis (1, 2). The onset of illness having this antibody is often rapid, with any combination of symptoms, including fever, polyarthritis, inflammatory myositis, Raynaud's phenomenon, "mechanic's hands", and interstitial lung disease (ILD) (1).

Myositis patients with anti-Jo-1 antibody have a poor prognosis and frequent relapses. These patients initially respond well to corticosteroids, but often relapse during tapering of the agent, and thus immunosuppressive agents such as azathioprine, methotrexate, and cyclophosphamide are frequently needed to control the disease (3). Despite aggressive immunosuppressive treatment, some patients could die of the progressive disease (4). Methotrexate and azathioprine have been widely used with corticosteroids for those patients, and the efficacy of combination of these two agents was reported

(5). In addition, the therapeutic effects of cyclosporine have been described in treatment-resistant myositis. Although the combined use of cyclosporine and methotrexate in refractory polymyositis was reported to be successful (6), it has not been described in refractory subgroup of patients with anti-Jo-1 antibody. We report a 32-yr-old female patient with polymyositis and anti-Jo-1 antibody. The disease was initially refractory to multiple immunosuppressive agents, but it was eventually controlled by combination treatment of cyclosporine and methotrexate.

CASE REPORT

In March 2000, a 32-yr-old woman was admitted with a one-month history of polyarthralgia and shortness of breath on exertion. She had not had weight loss, fever, alopecia, oral ulcer, or Raynaud's phenomenon. There was no past history of specific drug ingestion, smoking, abuse of alcohol, or environmental toxin exposure. On physical examination, inspiratory crackles were heard on both lower lung fields, and heart sounds were normal. An inflammatory polyarthritis affecting small joints of both hands and both knees was noted. Her fingers were those of the "mechanic's hands". However, the proximal muscle weakness and tenderness were absent.

Initial laboratory studies showed elevated levels of muscle enzymes, including creatinine kinase (CK) 1,895 U/L (normal

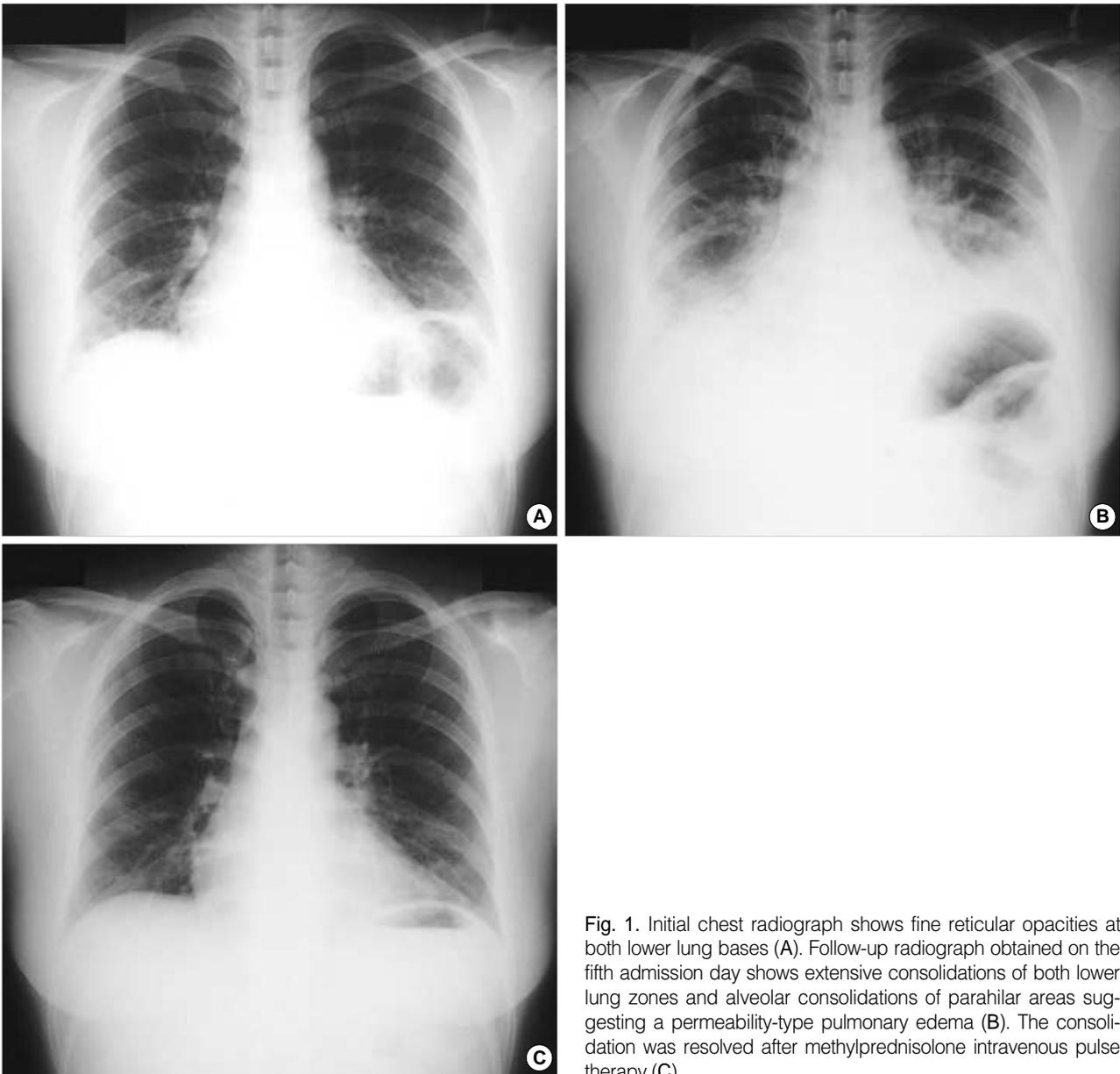


Fig. 1. Initial chest radiograph shows fine reticular opacities at both lower lung bases (A). Follow-up radiograph obtained on the fifth admission day shows extensive consolidations of both lower lung zones and alveolar consolidations of parahilar areas suggesting a permeability-type pulmonary edema (B). The consolidation was resolved after methylprednisolone intravenous pulse therapy (C).

<250 U/L) and lactate dehydrogenase 735 U/L (normal <420 U/L). The erythrocyte sedimentation rate was 20 mm/hr, and the C-reactive protein level was 1.89 mg/dL. The rheumatoid factor was negative and the antinuclear antibody titer was 1:320 with a cytoplasmic pattern. Anti-Jo-1 antibody was positive. There were no specific abnormal data on other chemistry profiles and immunological studies. A chest radiograph revealed bibasilar reticular changes consistent with ILD (Fig. 1A). High resolution CT scan showed reticular interstitial infiltrates with ground-glass opacities suggesting an active inflammation. Pulmonary function test revealed a mixed restrictive and obstructive pattern with a forced vital capacity of 56% of predicted, forced expiratory volume in 1 second of 57% of predicted, and carbon monoxide diffusing capacity of 64% of

predicted. Bronchoalveolar lavage showed 12% neutrophils, 38% lymphocytes, and 50% macrophages. Transbronchial lung biopsy could not be performed due to dyspnea. Cultures for bacteria, fungus, and mycobacteria were negative. There was no evidence of myositis on the magnetic resonance imaging (MRI) of both thighs (Fig. 2A), or on electromyographic examination of the extremities.

The diagnosis of antisynthetase syndrome with subclinical myositis was established. On day 5 of hospitalization, dyspnea was suddenly aggravated. Tachypnea and high fever were developed. The arterial blood gas analysis without O₂ supplementation showed PaCO₂ of 24.2 mmHg, PaO₂ of 69.7 mmHg, and O₂ saturation of 93.2%. Extensive pulmonary consolidations and permeability-type pulmonary edema resembling

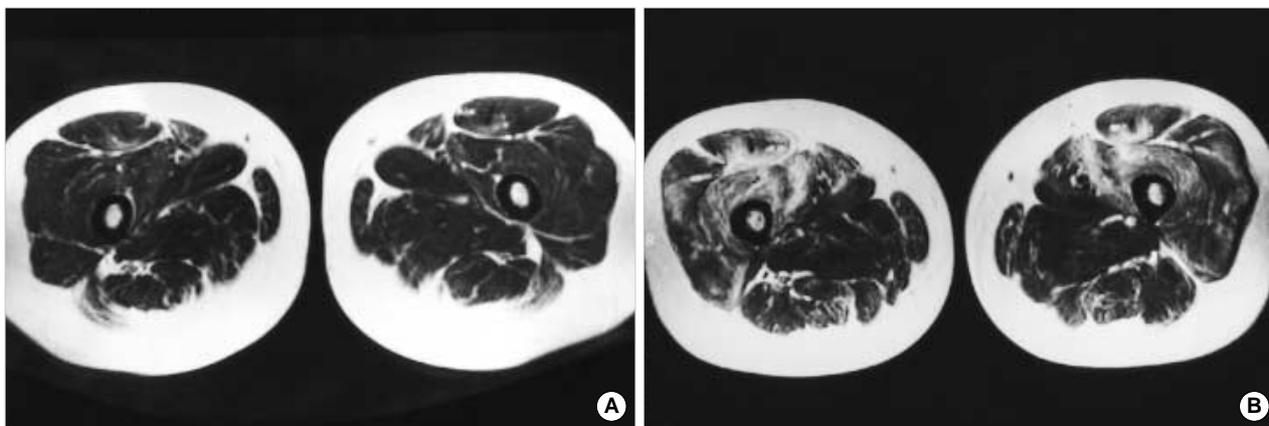


Fig. 2. There were no significant muscular signal abnormalities on the initial T2-weighted, magnetic resonance imaging of both thighs performed on admission (A). Follow-up scanning of the same locations shows bilateral symmetric, high signal intensity of thigh muscles except for adductor muscle groups suggestive of inflammatory myositis (B).

acute respiratory distress syndrome (ARDS) were noted on the chest radiograph (Fig. 1B). Her symptoms of dyspnea, fever, and polyarthralgia were subsided with intravenous (IV) pulse methylprednisolone (500 mg/day for 3 consecutive days). Subsequently, monthly IV pulse cyclophosphamide (500 mg/m²) and prednisolone 1 mg/kg/day (50 mg/day) were started. Azathioprine 1 mg/kg/day (50 mg/day) was added. The pulmonary consolidations on the previous chest radiograph were almost cleared (Fig. 1C), and the CK level was decreased to 512 U/L.

In the late April 2000, she noted the difficulty in raising both arms, and in climbing stairs, when prednisolone was tapered to 35 mg/day. The CK level was increased to 6,090 U/L. The findings of the follow-up MRI of both thighs (Fig. 2B) and the muscle needle biopsy specimen were consistent with inflammatory myositis. The prednisolone and azathioprine were increased to 50 mg daily and 75 mg daily, respectively. The monthly IV cyclophosphamide pulse therapy was continued. One month later, the muscle weakness was not improved, and the CK level did not decrease below 4,000 U/L. Furthermore, on the next month, a life-threatening sepsis occurred, which was successfully treated.

In the early July 2000, prednisolone 30 mg/day and cyclosporine 4 mg/kg/day (200 mg/day) instead of cyclophosphamide and azathioprine were prescribed. During the next four months, in spite of these medications, the CK level did not decrease below 4,000 U/L, with a persistent muscle weakness. In November 2000, methotrexate 10 mg/week was added to cyclosporine, and gradually increased to 17.5 mg/week. After 2 months, the CK level was decreased below 1,000 U/L, and the muscle strength gradually began to improve. Prednisolone could be reduced to 15 mg/day. In March 2001, the level of muscle enzymes was in the normal range (CK 55 U/L, LDH 334 U/L), and the muscle strength was gradually restored. Prednisolone was successfully tapered to 5 mg/day. The follow-up chest radiograph and pulmonary function test were

almost returned to normal.

DISCUSSION

Myositis patients with any of antisynthetase antibodies have a high frequency of ILD. Several other clinical features besides lung involvement and inflammatory myositis are more common in myositis patients with antisynthetases, including fever, inflammatory polyarthritis, Raynaud's phenomenon, and "mechanic's hands". This disease entity is referred to as the "antisynthetase syndrome" (1, 7). In our case that the diagnosis of antisynthetase syndrome with anti-Jo-1 antibody was made, the lung involvement resembling ARDS initially occurred, and the findings suggestive of clinically overt myositis were absent except the elevation of muscle enzymes. Subsequently, she developed an overt myositis during the tapering of prednisolone.

Even though corticosteroids remain the agent of choice for the initial treatment of IM, their use causes many adverse effects. The immunosuppressive agents such as azathioprine, methotrexate, cyclophosphamide, or cyclosporine have been increasingly used with corticosteroids in patients with rapidly progressive illness having serious extramuscular manifestations, disease relapses with the reduction of corticosteroids, serious corticosteroids-related complications, or the disease refractory to corticosteroids only (3). Because the prognosis of patients with IM relies on early diagnosis and treatment (8), the concomitant use of such agents with corticosteroids may be considered at an early stage of the disease.

Interstitial pneumonitis is a serious complication of IM, and considerably influences the patient's prognosis. Once fibrosis is established, the disease is resistant to treatment. So immunosuppressive agents are necessary when the inflammatory, ground-glass phase predominates (3). A prospective trial of IV pulse cyclophosphamide was effective in six patients with

rapidly progressive ILD including 2 patients with polymyositis (9). The efficacy of cyclosporine in IM has been described in progressive ILD (4, 10) as well as in the primary muscle involvement. In addition, Tellus et al. reported a patient with anti-Jo-1 positive refractory polymyositis and ILD who was successfully treated with cyclosporine (11).

The rapidly progressive lung disease of our patient was effectively treated with methylprednisolone pulse therapy and immunosuppressive agents, and her lung disease has been stable until now. However, the overt myositis occurred during the tapering of prednisolone. The muscle weakness and the elevation of muscle enzymes were refractory to the high-dose prednisolone and several immunosuppressive agents such as azathioprine, cyclophosphamide, and cyclosporine. Beneficial effects of methotrexate have been reported in patients with IM (8), but this agent was initially avoided as treatment regimen because of its potential pulmonary toxicity in the case with preexisting lung disease. After all, the muscle strength and muscle enzyme levels were restored when methotrexate was cautiously added to cyclosporine. Mitsunaka et al. reported on the successful combined use of cyclosporine and methotrexate in a patient with treatment-resistant polymyositis, in whom anti-Jo-1 antibody was negative (6). The combined use of these two agents in refractory myositis with anti-Jo-1 antibody has not to our knowledge yet been described.

The combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis has been proven effective and relatively well tolerated (12, 13). In addition, this combination therapy seemed to be effective and also well tolerated in refractory juvenile rheumatoid arthritis and juvenile dermatomyositis (14). To date, the experience of such a treatment in refractory myositis is very limited, and the combined treatment of cyclosporine and methotrexate should be urgently considered for future studies.

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