Successful Treatment with Tacrolimus in a Case of Refractory Dermatomyositis

Key words: Rhabdomyolysis, Ileus, Plasma exchange, IVIG, refractory

Idiopathic inflammatory myopathies are divided into three major groups: polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM). Although most patients with PM or DM respond well to corticosteroids, 20–30% of cases show an unsatisfactory response and other therapeutic options need to be considered (1). Here, we report a patient with severe DM complicated with rhabdomyolysis and paralytic ileus. Combined treatment with corticosteroids, intravenous immunoglobulin (IVIG) and plasmapheresis initially showed beneficial effects. However, the response was incomplete and he had relapses after the initial treatment. Therapies were then changed to oral administration with tacrolimus, which showed favorable effects.

Case Report

A 31-year-old man was diagnosed as having dermatomyositis (DM). He had been treated with intravenous pulse methylprednisolone (1 g/day for 3 days) followed by oral prednisolone (0.8 mg/kg/day) since May 23, 2001. In addition, methotrexate therapy (50 mg/wk) was started. His serum CK level initially decreased from 21,150 IU/l to 12,270 IU/l but rose to 16,950 IU/l on June 4. His urine was red and urinary myoglobin increased to 262,000 ng/ml. He became wheelchair-bound and complained of dysphagia. He was transferred to Tokushima University Hospital on June 7. On admission, erythema and edema of subcutaneous tissue in eyelids, periungual skin and extensor surfaces of the knuckles, elbows, and knees. Furthermore, he exhibited a paralytic ileus and respiratory disturbance. Neurologic examination demonstrated prominent weakness in facial muscle and neck flexors as well as in proximal limb muscles. Antinuclear and anti-DNA antibodies were positive (1 : 1,280 and 13 IU/ml, respectively), but anti Jo-1 antibody was negative. An electromyogram showed myopathic motor unit potentials with a low amplitude and short duration in deltoid muscle and biceps muscles. Denervation potentials, including fibrillation potentials and/or positive sharp waves, were also observed in those muscles. Biopsy of the right quadriceps was performed. Biopsied muscle showed regenerating/degenerating changes and prominent infiltrates of mononuclear cells around small vessels and muscle fibers. In addition, muscle fibers were mildly atrophic in perifascicular regions. Due to resistance to initial corticosteroid therapy and the presence of rhabdomyolysis, double-filtration plasmapheresis (DFPP) was performed on June 15. His skin rash and abdominal symptoms partially improved, and these improvements were followed by decreases in serum CK and urine myoglobin levels. Since the response was incomplete combined treatment with corticosteroids, DFPP and IVIG (400 mg/kg/day for 5 days) was performed in July and August. In September, his symptoms were well controlled and levels of CK and urine myoglobin had improved to 905 IU/l and <5 ng/ml, respectively. The clinical picture has previously been reported (2).

In 2002, his serum CK level increased again, followed by a deteriorating Medical Research Council (MRC) score, corresponding to a muscle strength of 18 proximal muscle groups (maximal score was 90) (3). From this time, myositis remained active with deterioration in muscle strength or relapses, despite repeated therapies of pulse methylprednisolone, IVIG and DFPP (Fig. 1). Oral administration with tacrolimus (3 mg/day) was introduced in May 2003. Serum CK levels steadily decreased, with an increase in MRC score. Relapse of symptoms was not observed during tacrolimus treatment (from May 2003 to February 2004). Plasma tacrolimus levels ranged from 4 to 8 ng/ml and no adverse effects were observed, including blood glucose levels and renal function.

Discussion

The present patient exhibited severe DM complicated with rhabdomyolysis and paralytic ileus. Rhabdomyolysis seemed to be associated with DM because it disappeared after the induction therapy for DM. In addition, various underlying conditions were not suggested by the laboratory data or the history of illness, including metabolic defects, intoxication, infections and crush injury. Paralytic ileus is a rare complication of PM/DM but it is noteworthy that the complication is usually refractory to corticosteroids (4, 5). Since rhabdomyolysis and paralytic ileus are life-threatening complications, it was very important for the patient to search effective therapies.

Although the causes of PM, DM, and IBM are unknown, autoimmune mechanisms are implicated in the development of muscular lesions. Most patients with PM and DM respond satisfactorily to corticosteroids. However, in a proportion of patients (20–30%) with PM or DM corticosteroid therapy is resistant and it is necessary to introduce a second-line agent. IVIG therapy and plasma exchange synchronized with IVIG have been shown to be effective in some cases of intractable PM/DM (3). Combination therapy with corticosteroids, IVIG and plasmapheresis initially showed beneficial effects but not enough to control the myositis. In contrast, tacrolimus therapy combined with prednisolone (20 mg/day) showed
Tacrolimus and cyclosporin A potentially suppress antigen recognition by T cells by inhibiting not only calcineurin but also JNK/p38 kinase (6, 7). Tacrolimus is known to be 10–100-fold more active than cyclosporin A in all parameters of specific T cell inhibition (6, 7). Recently, Utsugisawa et al reported that this treatment was significantly effective in MG patients with high IL-2 productivity in peripheral blood mononuclear cells (PBMC) (8). They reported that clinical improvement with tacrolimus was achieved so rapidly that lower-limb muscle strength improved 2 weeks after the start of administration. Methotrexate, a commonly used second-line agent for myositis, was not effective to control myositis in the present patient. We then tried to treat with tacrolimus in addition to prednisolone. Only a few reports have described the beneficial effects of systemic administration of tacrolimus in patients with DM (9), although topical tacrolimus therapy has been effectively applied to skin lesions (10). Oddis et al reported the beneficial effects of tacrolimus in PM with interstitial pneumonitis (11). Tacrolimus was effective against myositis as well as extra-muscular symptoms including pulmonary function. These findings as well as the observations reported here indicate that tacrolimus has the potential for therapy of steroid-resistant DM.

Figure 1. Clinical course of the patient (31-year-old man), repeatedly treated with combined therapy including intravenous pulse methylprednisolone (mPSL, 1 g/day for 3 days), oral prednisolone (40–20 mg/day), double-filtration plasmapheresis (DFPP), and intravenous immunoglobulin (0.4 g/kg). Serum CK levels initially decreased followed by an improved Medical Research Council (MRC) score corresponding to proximal muscle strength. In 2002, his serum CK level and MRC scores were not improved despite repeating the combination therapy. Oral administration with tacrolimus (3 mg/day) was introduced in May 2003. Serum CK levels steadily decreased with increase in MRC score. Plasma tacrolimus levels ranged from 4 to 8 ng/ml.
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