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【 CASE REPORT 】

Anti-MuSK Antibody-positive Myasthenia Gravis Successfully Treated with Outpatient Periodic Weekly Blood Purification Therapy

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Abstract:
A 37-year-old man with anti-muscle-specific tyrosine kinase (MuSK) antibody-positive myasthenia gravis (MG) presented with subacute progressive dysphagia and muscle weakness of the neck and bilateral upper extremities. Conventional immune-suppressive treatments and high-dose intravenous immunoglobulin were ineffective. He then displayed repeated exacerbations and remissions over the course of two years, despite two to four sessions of plasma exchange (PE) every two months. The patient was successfully treated with outpatient periodic weekly blood purification therapy with alternative PE and double-filtration plasmapheresis using an internal shunt. This case report suggests the benefits of blood purification therapy with an internal shunt against anti-MuSK antibody-positive MG.

Key words: myasthenia gravis, periodic weekly blood purification therapy, anti-MuSK antibodies

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Introduction

Myasthenia gravis (MG) is an autoimmune neurological disorder associated with antibodies for acetylcholine receptor (AChR). However, approximately 20% of patients with generalized MG do not have detectable levels of anti-AChR antibodies (1). Furthermore, about 70% of anti-AChR-antibody-seronegative MG patients have serum autoantibodies for muscle-specific tyrosine kinase (MuSK) (2, 3). MuSK plays an important role in agrin-mediated clustering of AChR at the endplate (3). Anti-MuSK antibodies mainly belong to the immunoglobulin-G4 (IgG4) subclass, which decrease the clustering of AChR, resulting in abnormalities in electrophysiological neuromuscular junctions (4). Anti-MuSK antibody-positive MG (MuSK-MG) patients show various responses to cholinesterase inhibitor, oral high-dose daily prednisolone (PSL), azathioprine, cyclosporin A, mycophenolate mofetil, intravenous immunoglobulin (IVIG) (5), rituximab (6), and plasma exchange (PE) (7) but respond poorly to thymectomy (8-11). Although conventional immunosuppressants are effective in most MuSK-MG patients, some patients respond poorly or are unable to continue these therapies due to adverse effects.

We herein report the course and outcome of a patient with MuSK-MG treated with periodic weekly blood purification therapy.

Case Report

A 37-year-old Japanese man subacutely developed dysphagia, muscle weakness of the neck and bilateral upper

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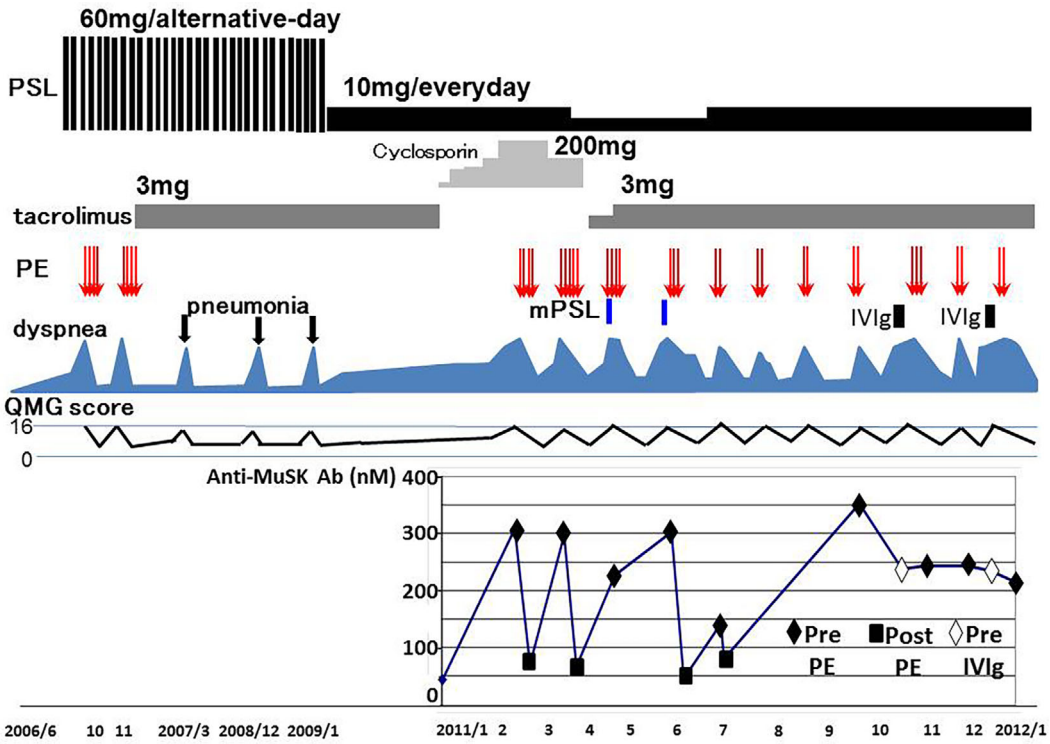

Figure 1. **Clinical course before periodic weekly blood purification therapy. Note the initial benefit of plasma exchange (PE) for both the symptoms and anti-muscle-specific tyrosine kinase (MuSK) antibody level, which became ineffective in later years despite the administration of intravenous immunoglobulin (IVIg). Anti-MuSK antibodies were measured immediately before PE (Pre PE), immediately after PE (Post PE), or immediately before IVIg (Pre IVIg). mPSL; Methylprednisolone, PSL: prednisolone**

extremities, and dyspnea within 4 months. Due to the dyspnea, he became physically inactive and was admitted to Okayama University Hospital in October 2006 for the first time.

Physical and neurological examinations showed bilateral external ophthalmoplegia with mild abduction, dysphagia, dysarthria, mild muscle weakness of the neck and bilateral proximal upper extremities without atrophy, and severe dyspnea (MGFA classification; IIIb, QMG score; 16). His lung capacity decreased to 1.4 liters in terms of forced vital capacity, giving a predicted value of 31.5% of the full forced vital capacity. Repetitive nerve stimulation at a frequency of 3 and 5 Hz of the right ulnar nerve showed a decrease in the compound muscle action potential (CMAP) of 24.3% and 28.4%, respectively. His lung capacity improved slightly after edrophonium was administered. Blood biochemical tests showed an elevated anti-MuSK antibody level at 6.03 nM [cut-off value=0.05 nM; measured by Motomura et al. (11, 12)]. After four sessions of PE replaced by albumin, his symptoms improved dramatically [quantitative myasthenia gravis (QMG) score; 4], followed by oral PSL at a dose of 60 mg administered on alternative days.

However, his symptoms relapsed one month after serial PE. He was administered four sessions once again, with PE replaced by albumin, followed by 3 mg of oral tacrolimus in addition to PSL at a dose of 60 mg administered on alternative days. Although he maintained a stable physical state for half a year, he suffered from severe bacterial pneumonia three times between March, 2007 and January, 2009. Even though oral PSL was reduced to 10 mg every day, his respiratory function deteriorated (QMG score 7-8). Switching the immunosuppressant agent from oral tacrolimus to cyclosporine was not effective. He displayed repeated exacerbations and remissions over the course of the next two years, despite the administration of two to four sessions of PE every two months. An intravenous injection of methylprednisolone pulse therapy (mPSL; 1,000 mg, 3 days) and immunoglobulin (IVIg; 400 mg/kg, 5 days) was also not effective. As Fig. 1 shows, frequent biochemical blood tests revealed that the level of anti-MuSK antibody [cut-off value 0.01 nM; measured by Ohta et al. (7)] reflected the severity of his dyspnea. Anti-MuSK antibodies were measured immediately before PE (Pre PE), immediately after PE (Post PE), immediately before IVIg (Pre IVIg), and immediately after double-filtration plasmapheresis (DFPP) (Pre DFPP).

In April 2012, an internal shunt was created in his right forearm for frequent outpatient PE therapy. A weekly session of PE or two sessions of PE every three weeks improved his symptoms for about four months, after which PE was changed to DFPP as blood purification therapy. Since his symptoms remained good, PSL and tacrolimus were gradually decreased. However, his dyspnea was once again

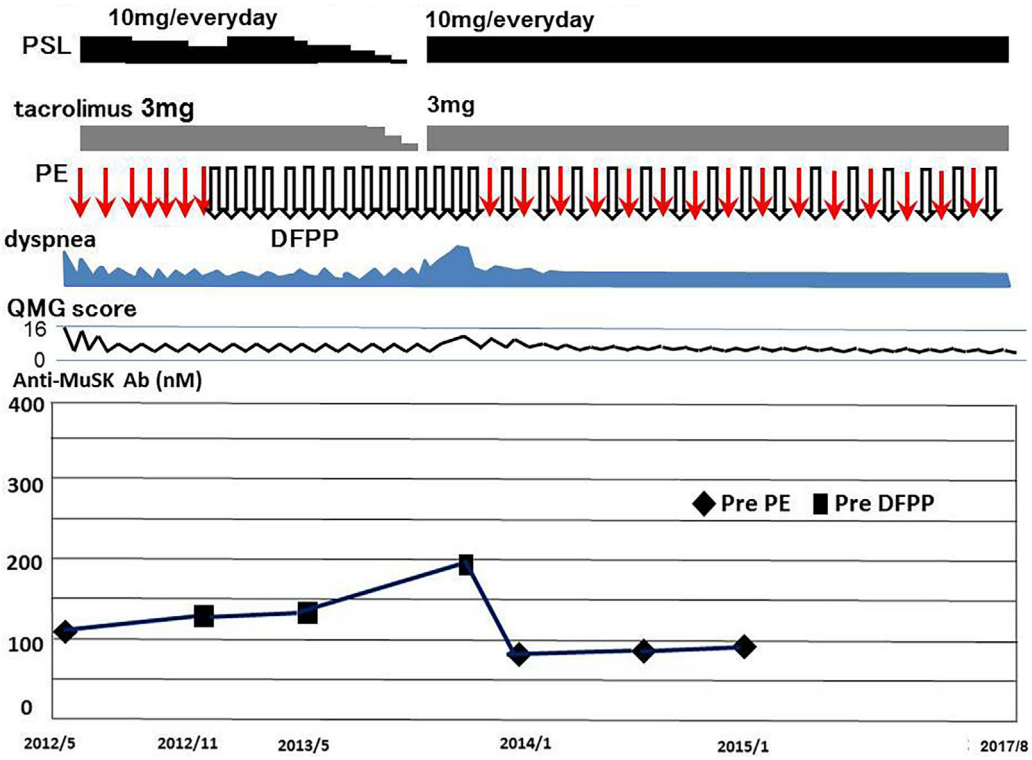

Figure 2. **Clinical course after periodic weekly blood purification therapy, showing improvement in the patient's symptoms, such as dyspnea, with a lower level of anti-muscle-specific tyrosine kinase (MuSK) antibodies than was achieved with occasional blood purification therapy. Note that changing weekly plasma exchange (PE) to double-filtration plasmapheresis (DFPP) was required to improve his symptoms and anti-MuSK antibody level at the later stage. Anti-MuSK antibodies were measured immediately before PE (Pre PE) or immediately after DFPP (Pre DFPP). PSL: prednisolone**

exacerbated (QMG score 12). Although the amount of these drugs was restored, his dyspnea did not improve. After a weekly alternation between PE and DFPP, his dyspnea finally improved, and the patient returned to his job (QMG score 4-5). The variation in the anti-MuSK antibody level almost disappeared after periodic blood purification therapy with alternative PE and DFPP (Fig. 2).

Discussion

We experienced a patient with MuSK-MG who presented with subacute progressive dysphagia and muscle weakness of the neck and bilateral upper extremities. The effect of blood purification therapy was evaluated based on the titer transition of the anti-MuSK antibodies as well as by the clinical symptoms, such as the respiratory function. In addition, the patient was successfully treated with periodic weekly blood purification therapy with alternative PE and DFPP, using an internal shunt created in his right forearm, although the patient resisted treatments such as steroid, tacrolimus, cyclosporine, and IVIg.

Steroids alone (13) or combined with an immunosuppressant, such as azathioprine (14), cyclosporine (15), or tacrolimus (16), are generally effective for treating MuSK-MG. Indeed, Shibata-Hamaguchi et al. reported that patients treated with IVIg showed good outcomes over a long period of time (5). However, MuSK-MG patients show variable responses to such conventional immunosuppressive treatment, and some are resistant to these therapies. The dose of steroids needed to maintain MuSK-MG may be higher than that for anti-AChR antibody-positive MG patients (17). In our case, high-dose steroid therapy was not successful due to increasing susceptibility to infection.

Some patients with severe generalized anti-AChR antibody-positive MG are resistant to anticholinesterases, thymectomy, corticosteroids, and azathioprine but responsive to PE (18). However, the effectiveness of PE in this report was only transient, and periodic PE treatments were necessary. In addition, long-term periodic PE treatments at a rate of two or three sessions every two weeks for an eight-year follow-up period have been performed for anti-AChR antibody-positive MG patients who were resistant to anticholinesterases, thymectomy, corticosteroids, azathioprine, and IVIg (19). Although we followed our MuSK-MG patient with periodic weekly blood purification therapy with alternative PE and DFPP for about five years, no side effects related to PE, DFPP, or vascular access (i.e. a fever, infections, cardiac arrhythmias, or bleeding diathesis) were observed, unlike in the two previous reports.

DFPP was reported to be as effective as PE for anti-MuSK antibody removal and the amelioration of clinical weakness (20). In the present case, DFPP was administered

as a substitute for PE to reduce albumin consumption for two reasons: to prevent transfusion-transmitted diseases and to reduce medical costs. However, the administration of an alternate treatment between weekly PE and DFPP was ultimately required. MuSK-MG might also be associated with various disease agents other than anti-MuSK antibodies, such as certain cytokines, that cannot be removed by DFPP due to their low molecular weight (21).

This treatment carried some disadvantages for this patient, including the need for a surgically-placed internal shunt. As the patient easily entered a state of crisis without frequent blood purification therapy, he underwent surgery to facilitate vascular access in his forearm for weekly PE or DFPP. Internal shunts are associated with some complications, including infection, a cold feeling in the forearm, and heart failure due to volume overload (22). Considerable attention must therefore be paid to these shunt-related issues.

To our knowledge, this is the first report of a patient with anti-MuSK antibodies who was successfully treated by periodic weekly blood purification therapy with alternative PE and DFPP, using an internal shunt created in his right forearm. These findings suggest that periodic weekly blood purification therapy with alternative PE and DFPP may be a helpful and relatively safe treatment for MuSK-MG.

Written informed consent was obtained from the patient for the publication of this case report.

A copy of the written consent is available for review by the Editor-in Chief of this journal.

The authors state that they have no Conflict of Interest (COI).

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