Patient with Neuromyelitis Optica Spectrum Disorder Combined with Sjögren’s Syndrome Relapse Free Following Tacrolimus Treatment

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Abstract

Abstract Tacrolimus, a novel immunosuppressant agent, has been widely used in organ transplantation and autoimmune diseases. We herein present a case of neuromyelitis optica spectrum disorder (NMOSD) combined with Sjögren’s syndrome (SS) successfully treated with tacrolimus. This patient repeatedly presented with recurrent longitudinally extensive transverse myelitis. Her NMO-IgG and anti-SSA and anti-SSB antibodies were seropositive. Considering the frequency of relapses and severe disability, tacrolimus was initiated after failure of intravenous cyclophosphamide. Her status was steady for over 36 months after tacrolimus treatment. This report indicates that tacrolimus may be a potentially effective immunosuppressant for NMOSD with systemic autoimmune diseases.

Key words: tacrolimus, neuromyelitis optica, neuromyelitis optica spectrum disorder, cyclophosphamide, Sjögren’s syndrome


Introduction

Neuromyelitis optica (NMO) is an inflammatory demyelinating disease of the central nervous system (CNS) with a predilection of affecting the optic nerves and spinal cord (1). NMO is currently considered to be a syndrome with a wide spectrum of clinical manifestations, including classical defined NMO, limited forms of NMO, such as isolated longitudinally extensive transverse myelitis (LETM) and isolated recurrent optic neuritis (ON), and ON and LETM-associated with systemic autoimmune diseases (2). ON and LETM, though rare, can be presentations of Sjögren’s syndrome (SS) and other systemic autoimmune diseases. Therefore, the relationship between NMO or neuromyelitis optica spectrum disorder (NMOSD) and systemic autoimmune diseases has become complicated (3, 4). We herein report a patient meeting both of the criteria for NMOSD and SS, who was successfully treated with tacrolimus, thereby preventing relapses after the failure of intravenous cyclophosphamide treatment.

Case Report

A 32-year-old Chinese woman was admitted to our gastroenterology department presenting with intractable nausea, vomiting and hiccup without any prodromal infection in 2003. No definitive diagnosis was made after a series of gastroenterological tests. Her symptoms gradually improved after 1 month without any specific treatment. Two years later, nausea and vomiting occurred again within one month after an influenza infection. But this time, paraesthesia initially developed in her arms and then in her legs. Simultaneously, she had paralysis in her bilateral lower limbs. Subsequently, ptosis in her right eye and sphincter dysfunction developed. The clinical examination revealed moderate spasticity in the lower extremities. Cervical spinal cord magnetic resonance imaging (MRI) showed high-signal lesions on the T2-weighted image at the level of C5-T1 and medulla ob-
Steroid pulse therapy and a high dose of oral prednisolone were given. Although her symptoms gradually resolved, an adverse effect of femoral head necrosis occurred as evidenced by pain and a positive X-ray appearance in both hip joints. Consequently, glucocorticoid therapy was no longer indicated for her despite the frequent acrocyanesthesia and paraparesis episodes during the next two years. At the end of 2007, she suffered from a deteriorated episode with the symptoms of tetraplegia and urinary retention [expanded disability status scale (EDSS)=8.5, Fig. 1]. A cervical scan showed a high-signal lesion on T2-weighted MRI at the level of the upper cervical segment extending into the dorsal part of the medulla oblongata. Brain MRI showed a non-specific abnormality in the bilateral hypothalamus (Fig. 2). The blood examination revealed that anti-nuclear antibody (1:320), anti-SS-A antibody (1:640), and anti-SS-B (1:640) antibody were seropositive. However, no sicca symptoms were noted at this time. Anti-cardiolipin antibody and anti-neutrophil cytoplasmic antibody (ANCA) were negative. A high-dose of intravenous immunoglobulin (0.4 g/kg/d for 5 days) was given, and the neurological symptoms mildly improved. A NMO-IgG test was conducted and was seropositive. Considering her severe relapses and attack-related disability, intravenous cyclophosphamide monotherapy (0.8 g every 15-20 days for about 10 months) was started to reduce the frequency of her relapses. Unfortunately, her condition did not improve (Fig. 1). She still suffered from relapses and severe disability. She was eventually wheelchair-ridden. Hence, tacrolimus was initiated with the consent of the patient after the failure of intravenous cyclophosphamide treatment. She received tacrolimus over 3 years (2 mg daily for 1 year, 1 mg daily for 1.5 year, and 0.5 mg daily for 1 year). No significant adverse events were reported. Her condition was steady and no relapse occurred during a 3-year follow-up. With rehabilitation, her EDSS slowly decreased and she could manage to walk with assistance. For a more accurate diagnosis, careful consultation was conducted and mild sicca symptoms were later noticed by the patient. Schirmer’s test showed less than 5 mm in both eyes.

**Discussion**

Tacrolimus (FK506), a potent immunosuppressive agent inhibiting the action of calcineurin, is widely used as therapy for transplantation, skin disorders, allergies and autoimmune diseases (5). It inhibits CD4+ T cell activation and induces T cell proliferation and apoptosis. Recently, there have been many reports on the efficacy and safety of tacrolimus treatment for both adult and children with myasthenia gravis (6, 7). The immunosuppressive efficacy of FK 506 was demonstrated in experimental allergic encephalomyelitis, an animal model of multiple sclerosis (8). In the study of Kageyama et al., two NMO patients improved following tacrolimus treatment (9). In this study, we successfully prevented recurrent LETM episodes by tacrolimus treatment in a NMOSD and SS patient who was refractory to intravenous cyclophosphamide.

Although the patient did not present with ON, she showed frequent recurring LETM. Her NMO-IgG test was seropositive. Typical lesions of NMOSD in the dorsal part of the medulla oblongata and hypothalamus were also observed in our patient (Fig. 2). Therefore, the initial and following presentations of this patient fulfilled the criteria for NMOSD (10). In addition, her serum anti-nuclear antibody and anti-SSA and anti-SSB antibodies were positive. Later, the patient noticed mild sicca symptoms in her eyes and mouth. The result of Schirmer’s test further supported the diagnosis of possible primary SS (11). Therefore, our patient fulfilled the criteria for both NMOSD and primary SS.

![Figure 1. The expanded disability status scale (EDSS) of our patient followed about 7 years. In 2005, the EDSS was 6.0 after the first episode of misdiagnosing in 2003. The patient was often admitted to the hospital because of the frequent relapses or disabilities for further rehabilitation before tacrolimus was administered. During the treatment of intravenous cyclophosphamide, no improvement was seen. However, since tacrolimus was started, the EDSS was slowly decreased and steady. Besides, the patient was no longer admitted to the hospital since then.](image)
to prevent relapses, especially in patients with seropositive
immunosuppressive therapy is indicated in NMOSD over, NMO-IgG was correlated with the clinical status and 4 plays a central role in the pathogenesis of NMO. More severe disabilities. Recent studies have showed that aquaporin-4 plays a central role in the pathogenesis of NMO. Moreover, NMO-IgG was correlated with the clinical status and immunosuppressive treatment (14). There is no standard treatment for patients with both NMOSD and SS. Maintenance immunosuppressive therapy is indicated in NMOSD to prevent relapses, especially in patients with seropositive autoantibodies and longitudinally extensive lesions on the spinal cord MRI. Azathioprine is the current standard treatment for preventing NMO relapses. Other agents including mitoxantrone, cyclophosphamide, mycophenolate mofetil, and rituximab have been reported effective in reducing relapses in patients with NMO. However, only small observational studies have been conducted and the evidence level is only III (evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies) or IV (evidence from expert committee reports or opinions, clinical experience of respected authorities, or both). Monthly intravenous cyclophosphamide therapy is recommended for SS-related myelitis (15). However, our patient was unresponsive to intravenous cyclophosphamide monotherapy. This was similar to the report of Yaguchi et al. (16). In their study, case 1 worsened after intravenous cyclophosphamide treatment with a low dose of steroid. This unresponsiveness may indicate that the recurrence of LETM in our patient was not the vasculopathic complication of SS but was the limited form of NMOSD. With continuous treatment of tacrolimus for 3 years, the additive effects from previous intravenous cyclophosphamide monotherapy would be minimal or null. Tacrolimus is a macrolide with an immunomodulatory action similar to cyclosporine A but 10-100 times more potent. Our patient responded well to tacrolimus treatment and no side effects

reported (12). These studies indicate that NMO-IgG seropositivity signifies the coexistence of two autoimmune diseases rather than a secondary complication of the systemic disease. MRI findings in SS myelopathy may be similar to those of NMO, often being longitudinally extensive. In the brain MRI of SS patients, abnormalities in the periventricular and subcortical white matter are more common, and differ from the specific brain lesions of NMO/NMOSD patients. Thus, the clinical presentations of our patient could not be simply considered as a complication of SS.

The NMO-IgG test is required for LETM patients to confirm a more accurate diagnosis and for treatment decisions. NMO-IgG antibody is not present in the sera of systemic autoimmune disease patients without manifestations of NMO. Furthermore, NMO-IgG is a specific marker for NMO/NMOSD rather than a nonspecific coexisting serological finding associated with SS (13). Therefore, the patient was diagnosed with both NMOSD and SS. Positive NMO antibodies may indicate more frequent relapses and more severe disabilities. Recent studies have showed that aquaporin-4 plays a central role in the pathogenesis of NMO. Moreover, NMO-IgG was correlated with the clinical status and immunosuppressive treatment (14). There is no standard treatment for patients with both NMOSD and SS. Maintenance immunosuppressive therapy is indicated in NMOSD to prevent relapses, especially in patients with seropositive autoantibodies and longitudinally extensive lesions on the spinal cord MRI. Azathioprine is the current standard treatment for preventing NMO relapses. Other agents including mitoxantrone, cyclophosphamide, mycophenolate mofetil, and rituximab have been reported effective in reducing relapses in patients with NMO. However, only small observational studies have been conducted and the evidence level is only III (evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies) or IV (evidence from expert committee reports or opinions, clinical experience of respected authorities, or both). Monthly intravenous cyclophosphamide therapy is recommended for SS-related myelitis (15). However, our patient was unresponsive to intravenous cyclophosphamide monotherapy. This was similar to the report of Yaguchi et al. (16). In their study, case 1 worsened after intravenous cyclophosphamide treatment with a low dose of steroid. This unresponsiveness may indicate that the recurrence of LETM in our patient was not the vasculopathic complication of SS but was the limited form of NMOSD. With continuous treatment of tacrolimus for 3 years, the additive effects from previous intravenous cyclophosphamide monotherapy would be minimal or null. Tacrolimus is a macrolide with an immunomodulatory action similar to cyclosporine A but 10-100 times more potent. Our patient responded well to tacrolimus treatment and no side effects

Figure 2. Sagittal T2-weighted cervical spinal cord MRI shows a typical longitudinally extensive and swollen lesion that extends into medulla (A). Black hole is seen on T1-weighted image (B). Axial T2 weighted image of the spinal cord shows centrally located and transverse lesion (E). There are also patchy lesions in thoracic, lumbar, and even spine conus (C, D). Axial FLAIR image of the brain shows signal abnormality around the third ventricle, with extension into the hypothalamus (F). These lesions are more common and characteristic in NMO or NMOSD patients.
were observed. Therefore, our findings suggest that patients with combined autoimmune diseases and positive NMO-IgG antibody may need continuous immunosuppressant.

This case report suggests the application of tacrolimus in the immunosuppressive therapy for NMOSD and SS. Similar to the other immunosuppressants, tacrolimus may therefore be used as a monotherapy agent.

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

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