CASE REPORT

Pembrolizumab-induced Myasthenia Gravis Relapse after Immunosuppressive Therapy

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Abstract:
Myasthenia gravis (MG) is an immune-related adverse event (irAE), and as an irAE, MG (irAE-MG) generally has a monophasic course, with only a few case reports of irAE-MG flare-ups during the course of the disease. We herein report a case of pembrolizumab-induced MG with relapsing symptoms. irAE-MG is a rare disease that has not yet been fully characterized, and our case shows that MG symptoms may relapse. Therefore, regular follow-up is necessary, even after the symptoms improve with immunosuppressive therapy.

Key words: immunosuppressive, myasthenia gravis, pembrolizumab, an immune-related adverse event, relapse, recurrence

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Introduction

Pembrolizumab is an immune checkpoint inhibitor (ICI). It is a highly selective humanized monoclonal antibody (mAb) against programmed death-1 (PD-1) of the IgG4/k isotype. It activates T cells by inhibiting the binding of PD-1 to its ligand, thereby achieving antitumor effects. Although mAb against PD-1 is generally more effective than conventional chemotherapy, the activation of the immune system can cause immune-related adverse events (irAEs), such as skin disorders, gastrointestinal disorders, endocrine disorders, interstitial pneumonia, and neuromuscular disorders (1, 2). The incidence of myasthenia gravis (MG) as an irAE is low but, when it occurs, it is often severe (3, 4).

Guidelines for the treatment of irAEs have been published by the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) (2, 5). These recommend discontinuation of ICIs and immunotherapy with steroids, but no specific protocols or effective treatments have been suggested. The need for maintenance therapy is also unclear, as MG as an irAE (irAE-MG) is considered to have a monophasic course.

We herein report a case of irAE-MG with relapses. As with conventional MG, we believe that the possibility of relapse should be taken into consideration when selecting treatment for irAE-MG.

Case Report

A 74-year-old man was referred to our department with suspected pembrolizumab-induced MG (pMG). He had been diagnosed with bladder cancer eight years earlier. Three years before his visit to our department, he had undergone total cystectomy and ileal conduit because of bladder muscle layer invasion. Six months before his visit, computed tomography (CT) revealed para-aortic lymph node metastasis and left hydronephrosis. Five months before his visit, he was started on gemcitabine plus cisplatin, but his renal function deteriorated, and pembrolizumab was started one month later.

His blood creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) gradually increased after pembrolizumab treatment. There were no thoracoabdominal symptoms, muscle pain, or fatigue. He was examined by a gastroenterologist and a cardiologist to evaluate his CK levels and liver function, but neither hepatotoxicity nor myocardial impairment was found.

Pembrolizumab administration was continued, and the fifth course of pembrolizumab was scheduled one month before his visit to our department, but the treatment was dis...
continued due to the development of general fatigue and anorexia and an increase in CK levels to 2,155 IU/L. After the withdrawal of pembrolizumab, the CK levels improved, but ptosis of the left eyelid appeared. He was treated with 125 mg of intravenous (IV) methylprednisolone (mPSL) for 1 day due to suspicion of pMG. Since the ptosis had not improved, the patient was referred to our department the day after mPSL administration for a further investigation and treatment.

His symptoms intensified in the evening and showed daily fluctuation. He was admitted to our department immediately with suspected pMG. The patient had diabetes mellitus type 2, and he had undergone cholecystectomy and appendectomy for common bile duct stones and appendicitis, respectively. He had no personal history of autoimmune disease nor any family history of neuromuscular disease. He had smoked 2 packs of cigarettes per day between 20 and 60 years old but had stopped smoking completely. He drank about 1 L of beer per day until hospitalization.

The patient’s body temperature was 36.6°C, his blood pressure was 166/90 mmHg, his pulse was 95/min, his SpO2 was 95% (room air), and his respiratory rate was 24/min. Positive neurological findings included ptosis of the left eyelid that intensified in the evening, abduction of the left eyeball, and diplopia after 5 seconds of upward gazing with both eyes. No hoarseness was observed, but dysphagia was present. Light exertion caused fatigue and shortness of breath, but the patient was able to perform daily living activities independently. In the manual muscle test outline by the Medical Research Council, muscle strength was maintained at 5/5 in the trunk and all extremities. The patient was able to maintain head elevation in the supine position for 30 seconds, and his grip strength was 33.0 kg on the left and 28.8 kg on the right. There was no muscular atrophy or muscle pain. Deep tendon reflexes were normal, and there were no pathologic reflexes. There was no sensory disturbance. The patient’s quantitative MG (QMG) score was 14 points. According to the classification system of the Myasthenia Gravis Foundation of America (MFGA), the disease severity was Class IIb.

Blood tests showed mildly elevated AST (45 U/L), ALT (58 U/L), and CK (502 U/L). Other blood tests showed a white blood cell count of 101,000/μL, hemoglobin (Hb) levels of 14.6 g/dL, a platelet count of 22.1×10⁴ μL, C-reactive protein (CRP) levels of 0.20 mg/dL, blood urea nitrogen of 23.5 mg/dL, creatine (Cr) levels of 1.40 mg/dL, and glycated hemoglobin (HbA1c) of 6.0%. Tests for antinuclear antibodies, anti-aminoacyl-tRNA synthetases antibodies, anti-striated muscle antibodies, anti-acetylcholine receptor antibodies, and anti-muscle-specific tyrosine kinase antibodies were all negative. A cerebrospinal fluid (CSF) examination showed a total cell count of 12/μL with 8.3% neutrophils and 91.7% monocytes, CSF protein 34.6 mg/dL, and CSF glucose 86 mg/L. The abdution position of the left eye improved to the median position after administration of edrophonium in the tensilon test. Repetitive stimulation tests (RSTs) were performed on the left facial nerve, left accessory nerve, and right median nerve. The RST of the left facial nerve showed a decrease in amplitude of 8.7% at a stimulation frequency of 3 Hz, indicating a trend toward a waning phenomenon, although this was not significant. Needle electromyography (EMG) was performed on the left biceps brachii and right quadriceps. Polymorphic motor unit potentials with low amplitude were observed in the quadriceps, but neither resting spontaneous potentials nor early recruitment was observed. Electrocardiography and echocardiography showed no findings suggestive of myocardial damage. Magnetic resonance imaging (MRI) of the limbs showed atrophic changes in the right semimembranosus muscle with a high signal on T2-weighted imaging and an iso-signal on the short-tau inversion recovery sequence (Fig. 1). CT of the trunk showed atrophy and hydronephrosis of the left kidney and thickening of the upper tubular wall. No thymoma was detected.

Based on the symptoms and the result of the tensilon test, we diagnosed the patient with MG. Since the onset of symptoms occurred after treatment with pembrolizumab, we concluded that he had pMG. Oral prednisolone (PSL) (60 mg/day) was started on the day of admission, and intravenous immunoglobulin (IVIg) was administered for 5 days, beginning on the second day. On the eighth day of hospitalization, oral pyridostigmine was started. After treatment began, the patient’s CK rapidly decreased to within the reference range. Although his score on the QMG test of 14 before and 12 after treatment indicated no significant improvement, his subjective symptoms of fatigue, diplopia, and ptosis improved. Thereafter, PSL was gradually decreased, and IVIg was administered again in the fifth week of hospitalization, after which the patient was discharged.

He remained an outpatient for a while, but his ptosis, diplopia, and fatigue gradually worsened, so he was re-hospitalized four months after discharge and underwent further IVIg for symptom relief. CT of the trunk taken at this time showed enlargement of the right obturator lymph node, suggesting metastasis of the bladder cancer. This suggested that the cachexia of cancer might have aggravated his MG-induced fatigue. In the QMG scores before and on day 2 after five consecutive days of IVIg administration, his neck lifting time and right lower limb lifting time scores improved, but diplopia and the right upper limb lifting time scores worsened, and the total scores were not improved, which increased from 14 to 15 points. However, at one month after IVIg, his diplopia and fatigue were improved.

Two months after his last discharge, he was admitted to our department again, as he was becoming easily fatigued by mild exertion. At the time of admission, his CRP was high, at 17.48 mg/dL, and blood cultures showed that he was positive for extended-spectrum beta-lactamase (ESBL)-producing Escherichia coli. IVIg was administered, and meropenem treatment was started. The patient’s renal function deteriorated to serum Cr 2.29 mg/dL, and CT showed worsening of his lymph node metastasis. After the mero-
Figure 1. Magnetic resonance imaging of the muscles of the lower extremities. The right semimembranosus muscle was atrophic and exhibited a high signal on T2-weighted images (A, C) but showed an iso-intense signal on the short-tau inversion recovery sequence (B, D). These findings indicate fat replacement rather than muscular inflammation, which is consistent with the finding of necrotizing myopathy (12).

Figure 2. Clinical course. IVIg: high-dose intravenous immunoglobulin therapy, mPSL: methylprednisolone, Pem: pembrolizumab, PSL: prednisolone, Tac: tacrolimus

penem drip was replaced with oral minocycline, he was discharged. When the patient attended the outpatient clinic one week after discharge, his general condition had deteriorated, and his renal function had further worsened. He was readmitted and started on dialysis, but his condition deteriorated rapidly, and he died on the eighth day of hospitalization (Fig. 2). No autopsy was performed.

Discussion

We reported a case of pMG that showed partial improvement with immunosuppressive treatment followed by symptom relapse. MG is a disease characterized by easy fatigability due to disruption of the neuromuscular junction, and an immunological mechanism has been postulated. ASCO and ESMO have published guidelines for dealing with irAEs (2, 5). For irAE-MG, ICIs should be discontinued,
and the patient should be treated with immunosuppressive therapy, mainly steroids. Although irAE-MG is reportedly responsive to immunosuppressive therapy, it has a high mortality rate of 16.7-37% (3, 6, 7). The reason for the disparity between the high treatment efficacy and high mortality rate has not been elucidated. In our patient, the disease course suggested several factors that might bridge the gap between the conflicting data: irAE-MG relapse, the degree of treatment responsiveness, and the background characteristics of the patient.

Although immunosuppressive therapy for conventional MG can suppress the disease in many patients, some still suffer from relapse of symptoms during the course of the disease. In contrast, the published guidelines for irAE state that irAE-MG may be monophasic and thus do not mention the need for maintenance therapy (2, 5). In our case, although the patient had irAE-MG, he had a polyphasic disease course that relapsed after partial improvement with immunosuppressive treatment during the first occurrence of MG symptoms. We chose steroids and IVIg as immunosuppressive therapy during the onset of MG and IVIg as acute treatment during symptom flare-up. Although there was no significant improvement in the QMG scores before and after immunosuppressive therapy, the diplopia and fatigue improved. His fatigue may have been due in part to cachexia from cancer, but the fact that the symptoms improved even partially after IVIg is proof that there was a relapse of MG. Only a few cases of irAE-MG with symptom relapse have been reported, all of which were treated with the combination of ipilimumab and nivolumab (8, 9). To our knowledge, there have been no cases of recurrence of pembrolizumab inducing MG, making this case the first such report. Thus, we should be aware of the recurrence of irAE-MG as well.

For maintenance therapy, we chose oral prednisolone and tacrolimus. Prednisolone was started at a dose of 60 mg/kg followed by gradual dose tapering from weekly to monthly. The published guidelines recommend discontinuation of ICIs and initiation of immunosuppressive therapy, mainly steroids; however, no specific protocol is suggested. In our case, although few symptoms were suggestive of myositis, such as myalgia and weakness in the extremities, the CK level was elevated. Therefore, we decided on the treatment in the present case while considering not only MG but also inflammatory muscle disease. However, in our patient, relapse occurred despite maintenance therapy. Verma et al. reported a case of irAE-MG with a favorable outcome with repeated regular rituximab administration as maintenance therapy (8). There is no information on which patients are at an increased risk of recurrence or what the appropriate maintenance therapy protocol is; therefore, the accumulation of further cases and analyses are needed.

As mentioned above, our case showed only partial symptomatic improvement after immunosuppressive treatment. Suzuki et al. used the MGFA postintervention status in their report to evaluate the effect of immunosuppressive treatment on irAE-MG (3). Pharmacologic remission was observed in 2/12 patients, minimal manifestations in 2/12 patients, improvement in 5/12 patients, unchanged in 1/12 patients, and death in 2/12 patients. Thus, even if the patients were described as "steroid-responsive," there have been more than a few cases in which only a partial response was observed, which may be one reason for the disparity between treatment response and high mortality in irAE-MG.

It is necessary to consider the demographic data of patients as a factor contributing to the high mortality rate of irAE-MG. As a matter of course, patients who develop irAE-MG are those with carcinoma. It should be noted that when fatigue worsens in patients with irAE-MG, it is difficult to establish whether the symptoms are due to MG or cachexia caused by cancer, which was true in our case. Although we did not perform an autopsy on our patient, we suspected that his death was due to cancer progression, as blood tests a few days before death showed marked deterioration of the renal function, and CT showed enlarged metastatic lymph nodes and worsening hydronephrosis. Thus, cancer progression may influence the prognosis of irAE-MG. In this regard, there are some cases in which ICIs were restarted in patients who developed irAEs, with the expectation of improving their prognosis (7). While there have certainly been cases in which ICIs were restarted with a small dose of prednisolone (10), other studies have found that the progression-free period and overall survival can be prolonged by restarting ICIs only in patients who failed to achieve a partial response to ICIs before irAE (11). There is no consensus concerning the appropriate timing for ICI resumption in patients with irAEs, and more evidence is needed to establish this.

In the report of Huang et al. on irAE-MG cases, the mortality rate of irAE-related cases, excluding deaths due to cancer progression, was as high as 29.8% (6). When considering the prognosis of irAE-MG without the influence of cancer, the age of the patient cannot be ignored as a factor. Due to the nature of cancer, most patients who develop irAE-MG are also elderly (6, 7), so it may be natural that the mortality rate is higher than that of conventional MG.

Finally, multi-organ irAEs should also be considered as a prognostic factor. Among patients with irAE-MG, those with irAEs in other organs were suggested to have a poor prognosis (6). Thus, complications of irAE other than MG should be considered when determining the treatment of irAE-MG.

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

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