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Fatal triad of checkpoint inhibitors: Pembrolizumab induced myasthenia gravis with myositis and myocarditis in a patient with thymoma

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Abstract

Pembrolizumab is an immune checkpoint inhibitor that acts by blocking programmed cell death proteins, however, its use is limited in patients with thymoma. We describe a 31-year-old woman with thymoma who developed myocarditis, myositis and exacerbation of myasthenia gravis due to use of pembrolizumab. There were elevations of creatine phosphokinase, troponin T, CK-MB, alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase. Electrophysiologic studies showed a myopathic pattern and more than 10% decremental response on repetitive nerve stimulation. Steroid and intravenous immunoglobulin treatment was initiated. Because of a lack of improvement she received 5 cycles of plasma exchange. The patient benefited significantly from plasmapheresis and was discharged with noninvasive mechanical ventilation after one hundred and fifteen days of hospitalization. Plasmapheresis in the early period can be an effective treatment option in patients who develop severe neurological symptom with use of checkpoint inhibitors.

Keywords: Pembrolizumab, myasthenia gravis, miyositis, myocarditis, immune checkpoint inhibitor

INTRODUCTION

Immune checkpoint inhibitors (ICIs) can be associated with various neurologic immune-related adverse events (n-irAEs) such as encephalitis, transverse myelitis, myositis, blocking programmed cell death protein (PD-1) and has been used in various cancers.[4] Although cases of n-irAEs due to pembrolizumab use have been reported, coexistence of MG/myositis/ myocarditis is a rare and potentially fatal condition.[5]

Herein, we describe a patient with thymoma who developed myocarditis, myositis, and exacerbation of myasthenia gravis due to the use of pembrolizumab.

CASE REPORT

A 31-year old woman consulted to our clinic with refractory metastatic thymoma presenting with double vision, ptosis, dysarthria, dysphagia, weakness of the neck, and proximal dominant upper and lower limbs which started 18 days after a single dose of pembrolizumab. Seven years previously, she was diagnosed with acetylcholine receptor (AChR) antibody-positive ocular myasthenia gravis (MG) with double vision and unilateral drooping of the eyelid. Type B3 thymoma was detected, and she underwent mediastinal mass resection for thymoma, chemotherapy, and stereotactic ablative radiotherapy for metastases (the lung, pleura, mediastinum, and ribs). She had no history of other chemotherapies in the previous year and had been in pharmacological remission for MG for 5 years. In the follows up, metastatic lesions were found (pleura, mediastinum, and ribs) and as PD-L1 expression was detected in 100% of the tumor cells in the immunohistochemical examination of these metastatic lesions, a single dose of 200 mg pembrolizumab was administered to the patient. Physical examination revealed ptosis in the right eye, bilateral weakness of eye closing, bilateral horizontal and vertical gaze limitation, paresis in the bilateral facial muscles, bilateral hypoactive GAG reflex, dysphagia against fluids, hypophonic and nazone speech, and exertional dyspnea. Her muscle strength examination (MRC scale) revealed

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neck flexor and extensor 3/5, bilateral upper and lower limbs 3/5 proximal, and 4/5 distal. Deep tendon reflexes and sensory examination results were normal. The myasthenia gravis composite (MGC) score was 31 and the Myasthenia Gravis Foundation of America Clinical Classification (MGFA) score was Class IVb.

During the follow-up after pembrolizumab, laboratory tests showed creatine phosphokinase (CK), 10296 u/L (normal <170), troponin T; 1.51 μg/L (normal < 0.014), B-type natriuretic peptide (pro-BNP); 440 pg/mL (normal <125), D-dimer; 729 ng/ml (normal <500), CK-MB; 232 u/L (normal<25), alanine aminotransferase (ALT); 359 u/L (normal <33), aspartate aminotransferase (AST); 560 u/L (normal <32), lactate dehydrogenase (LDH); increased to 1431 u/L (normal<220) (Figure 1).

The AChR antibody level was found to be 1.02 nmol/L (normal <0.25). Tests for a anti-muscle-specific kinase (MuSK), anti-titin, anti-ryanodine, and myositis-associated antibodies were negative.

In 3 Hz repetitive nerve stimulation, more than a 10% decrement was obtained in the facial and ulnar nerves recorded from the nasalis and abductor digiti minimi muscles, respectively. Needle EMG examination revealed fibrillation potentials (FP) and positive sharp waves (PSW) in the bilateral tibialis anterior, gastrocnemius, rectus femoris, deltoid, biceps, forearm flexor, and extensor muscles at rest. Short duration and low-amplitude motor unit potentials with early recruitment were observed in these muscles.

In addition to elevated of troponin T, CK-MB, and pro-BNP levels in patients without chest pain, electrocardiography (ECG) revealed sinus tachycardia, negative T, and ventricular premature systole. Transthoracic echocardiography (ECHO), an ejection fraction (EF) of 60%. Supraventricular tachycardia was detected in Twenty-four hour holter monitoring. Myocarditis was diagnosed using electrocardiography (ECG) and cardiac marker follow-up. Pyridostigmine (300 mg/day) was administered orally at this dose. Intravenous immunoglobulin (IVIG) 0.4 g/kg/day was administered for five days. Intravenous methylprednisolone (64 mg, 1 mg/kg/day) was initiated and gradually increased to 125 mg. Ibuprofen (1800 mg/day) and ivabradine (10 mg/day) and diltiazem (90 mg/day) were administered to treat myocarditis. Intermittent noninvasive mechanical ventilation was applied to the patient

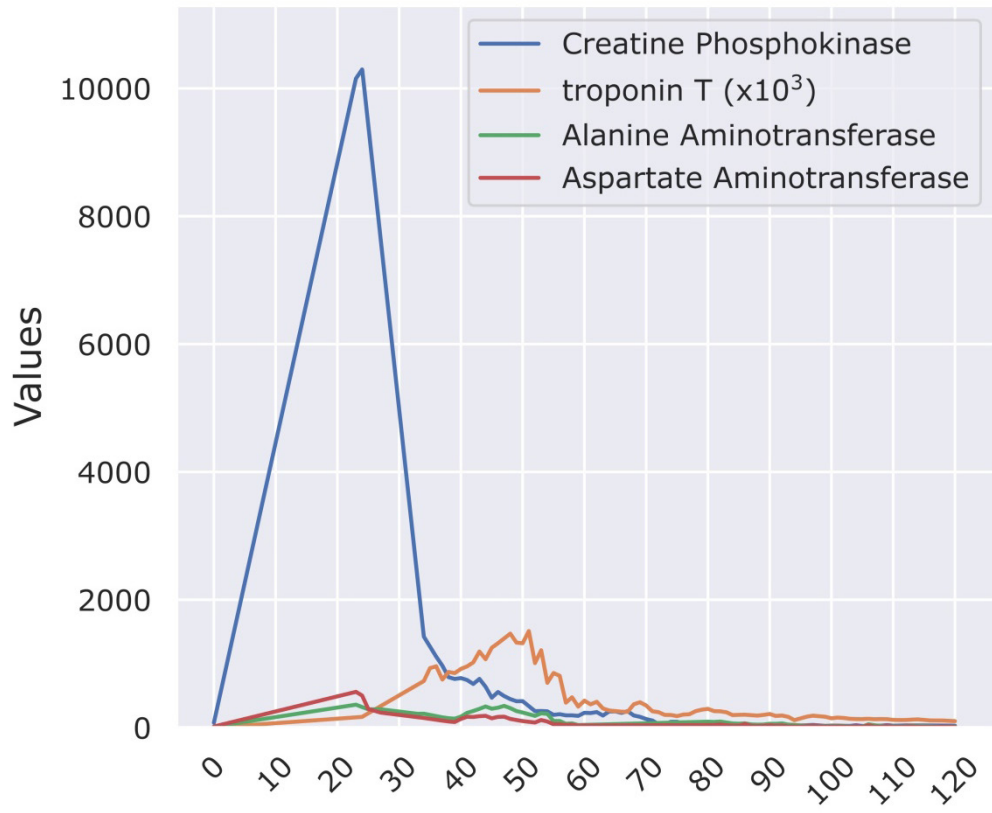

Figure 1. Blood biochemical parameters in the days after pembrolizumab administration.

with tachypnea. The patient did not respond well to treatment. As the troponin value continued to increase under this treatment and the MGC score increased to 43, plasmapheresis (PLEX) was administered 16 days after the end of IVIG treatment and considering the metastatic lesions, everolimus 2.5 mg/day was started (Figure 2).

After hundred and 15 days of hospitalization, the patient could swallow solid food and walk independently. Intermittent noninvasive mechanical ventilation was not required two months after discharge.

DISCUSSION

ICI-induced myasthenia gravis (ICI-MG) is an increasingly recognized complication of ICI therapy. While some cases involve exacerbations of pre-existing or subclinical MG, most cases represent de novo syndrome.[6]

Myositis can be associated with ICI-MG in up to 25% of patients, and its clinical presentation may resemble MG, which can present with ocular, bulbar, and respiratory symptoms.[6] It is important to recognize the overlapping features of ICI-myositis and ICI-MG, as the treatment of these two conditions may differ.[7]

In ICI-MG, antibody positivity against AChR is lower than that in classical generalized MG, and antibody titers are also lower.[7,8] The combination of anti-AChR antibodies and high CK levels makes it difficult to distinguish whether respiratory symptoms are due to MG or myositis, and electrodiagnostic tests may be helpful in this regard.[3,8] However, the characteristic EMG features of idiopathic MG can be detected in less than half of the ICI-MGs. Safa *et al*. performed electrophysiological examinations in 37 of 65 patients with ICI-associated MG patients, 13 of whom were previously diagnosed with MG. MG

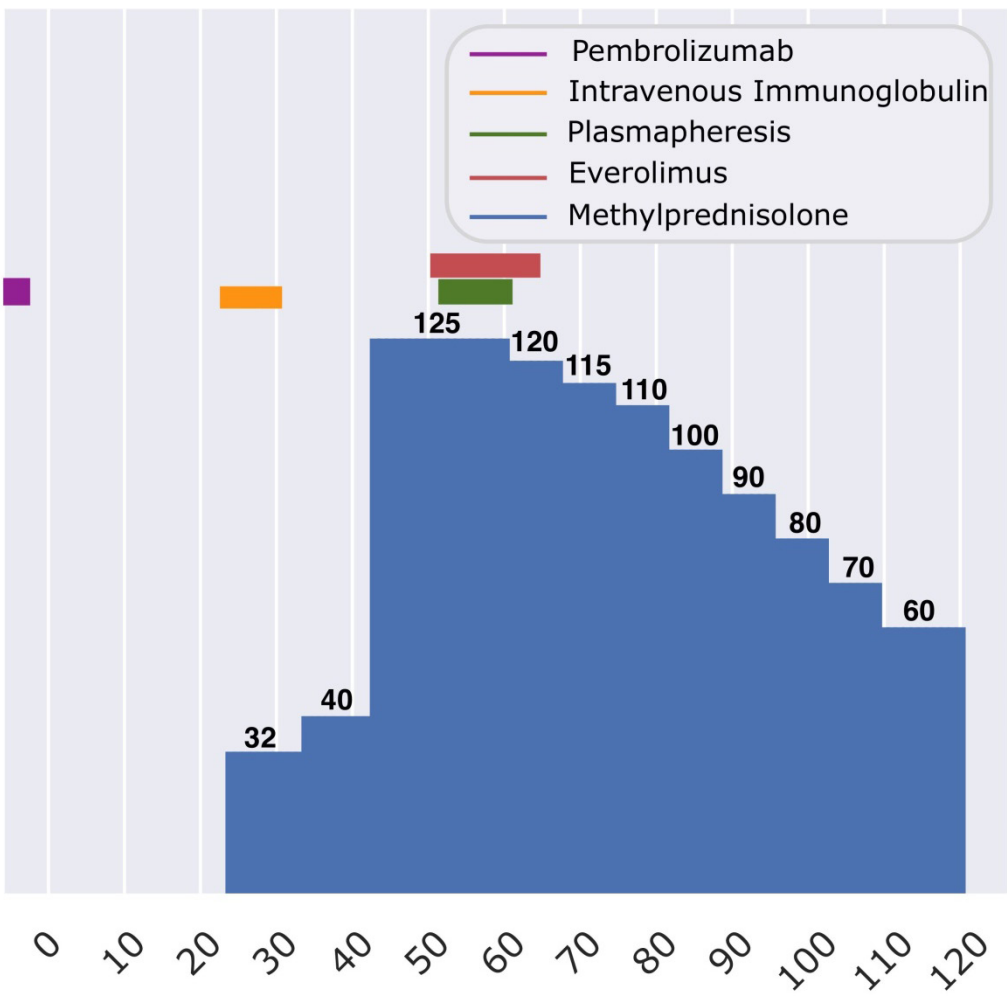

Figure 2. Treatment administration and dosing by days.

was found 41%, and MG and myopathy were found in 16% of them. Only two had a triad of MG/myositis/myocarditis.[3] In our case, AChR antibody and RNS tests performed after pembrolizumab treatment were positive. In addition, elevation of CK, AST, ALT, LDH, and myopathic patterns on EMG was consistent with ICI-related MG/myositis.

Concomitant myocarditis has been reported in approximately 8% of patients associated with ICI-MG.[3] Typical findings of myocarditis are new-onset arrhythmias and elevated troponin and creatine kinase (CK) levels.[9] While the most common findings on ECG are sinus tachycardia, ST elevations, and bundle branch blocks, there may be normal or decreased ejection fraction on echocardiography.[10] If necessary, cardiac imaging with MRI might be helpful for diagnosis confirmation.[9] Cardiac MRI could not be performed because metallic material was present in the paracardiac area secondary to the previous surgical operation for thymoma, which would have caused artifacts. A cardiac biopsy could not be performed because of the patient's general condition and respiratory problems. On detection of ventricular premature systole and T negativity on ECG, along with troponin T, CK, CK-MB, and pro-BNP elevation, in addition to MG and myositis, our patient was diagnosed with myocarditis.

The use of pembrolizumab in patients with thymoma is limited in the literature, and there have been two phase II studies[11,12] and some case reports.[13,14] In a phase II study by Cho *et al*., 26 of 33 patients had thymic carcinoma (TC), and seven of them had thymoma. After pembrolizumab treatment, two patients (28.6%) had a partial response and five (71.6%) had stable disease. Although pembrolizumab treatment was effective in patients with thymoma, the incidence of severe irAEs was higher than that in the TC group (71.4% vs. 15.4%); therefore, it was recommended to avoid the use of ICIs in patients with thymoma.[12]

Corticosteroids are the most commonly used first-line treatments. Although it is known that the use of steroids alone in the early period may paradoxically exacerbate the symptoms of myasthenia, higher doses of corticosteroids are required in these patients due to the more frequent myositis/myocarditis association compared to idiopathic MG.[3] Antiarrhythmic treatment was administered if arrhythmia was present.[15] Baseline and dynamic ECG, troponin, CK-MB, and cardiorespiratory symptoms should be carefully monitored for the early diagnosis and treatment of myocarditis.[16]

The clinical practice guidelines for the management of ICI-related MG recommend the addition of IVIG or PLEX as second-line treatment for patients presenting with severe symptoms or if patients had no improvement or worsening on steroid treatment alone (MGFA class III to V).[15] On the other hand, in a study, it was stated that patients who received IVIG or PLEX in treatment achieved better clinical improvement than those who received steroids alone, and it was stated that IVIG or PLEX initiation in the early period may be a better option regardless of the severity of the first symptoms.[3] Although our patient did not respond well to steroids and IVIG, there was significant improvement with PLEX.

In contrast to classical MG, immune-related MG (ICI-MG) tends to be life threatening, with higher rates of respiratory problems and death. A 60% mortality rate has been reported for myocarditis with myositis and/or myasthenia gravis.[5]

In conclusion, although pembrolizumab is a promising and effective treatment modality for thymic epithelial tumors, ICI-related myocarditis, myositis, and MG are life-threatening, high-grade complications. We believe that it would be beneficial for oncologists and neurologists to decide together on the initiation of pembrolizumab treatment for thymoma patients with a previous MG diagnosis. Autoimmune diseases secondary to ICI treatment should be diagnosed early and treated aggressively, using a multidisciplinary approach. In patients with severe symptoms, PLEX should be administered in the early period without delay.

DISCLOSURE

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