Simultaneous pembrolizumab-induced myasthenia gravis and myocarditis in a patient with metastatic bladder cancer: A case report

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\textbf{ABSTRACT}

We report a fatal case of pembrolizumab-induced myasthenia gravis and myocarditis in a patient with metastatic bladder cancer. A 77-year-old man was aware of eye ptosis and diplopia after three weeks from first infusion of pembrolizumab, an anti-programmed cell death protein 1 monoclonal antibodies. He was diagnosed with myasthenia gravis, because he was positive on the edrophonium test and acetylcholine receptor antibody. As his echocardiography also revealed diffuse loss in wall motion with ejection fraction 29%, he was strongly suspected myocarditis. Although he was treated with prednisone and intravenous immunoglobulin, he was suddenly in cardiac arrest and passed away.

\textbf{Introduction}

Pembrolizumab is an anti-programmed cell death protein 1 monoclonal antibody used to treat various malignant tumors. Though the incidence of pembrolizumab-related adverse events (AEs) is relatively low compared with that of other anticancer agents, various immune-related AEs (irAEs) can occur and become severe in some patients who received immune checkpoint inhibitors. We report a rare and fatal case of simultaneous myasthenia gravis (MG) and myocarditis in a patient with metastatic bladder cancer who had administered pembrolizumab.

\textbf{Case presentation}

A 77-year-old man visited a community hospital with chief complaints of macrohematuria and dysuria. Computed tomography (CT) showed multiple bladder tumors with pelvic lymph node involvement (Fig. 1). He underwent treatment with gemcitabine (1000 mg/m\textsuperscript{2} on days 1, 8, and 15) and cisplatin (70 mg/m\textsuperscript{2} on day 2) every 4 weeks. After three cycles of chemotherapy, CT showed progression of the bladder neoplasia and lymph node metastases. The patient then received pembrolizumab at a concentration of 200 mg every 3 weeks.

After 20 days of pembrolizumab treatment, the patient experienced right ptosis and diplopia. Laboratory evaluations revealed the following findings: aspartate transaminase 510 U/L (normal range: 13–30 U/L), alanine transaminase 223 U/L (normal range: 10–42 U/L), lactate dehydrogenase 1183 U/L (normal range: 124–222 U/L), creatinine phosphokinase 8574 U/L (normal range: 59–248 U/L), creatinine phosphokinase-myocardial band 207 U/L (normal range: <6 U/L), troponin T 9.28 ng/ml (normal range: <0.014 ng/ml), N-terminal pro-brain natriuretic peptide 6854 pg/ml (normal range: <125 pg/ml), creatinine 1.31 mg/dL (normal range: 0.65–1.07 mg/dL) and hemoglobin 9.2 g/dL (normal range: 13.7–16.8 g/dL). All other laboratory testing including virus tests were within normal limits. Magnetic resonance imaging of the brain and electrocardiogram were normal. He received 80 mg of prednisone daily due to the suspicion of irAE with hepatic dysfunction. After 4 days of steroid administration, he was diagnosed with MG by a neurologist using an edrophonium test. Simultaneously, an electrocardiogram showed ST elevation and left bundle branch block with a wide QRS, and echocardiography revealed diffuse loss in wall motion and 29% with ejection fraction. Based on these findings, he was diagnosed with heart failure secondary to myocarditis. Immediately, he was treated with intravenous immunoglobulin (IVIG) at 0.4 g/kg, given over five days, with daily administration of 80 mg of prednisone, along with dobutamine, carperitide, and furosemide.
He was transported to our hospital, because his symptoms and laboratory data did not improve with these treatments. He continued to be treated with IVIG for the remaining three days. A temporary pacemaker was placed to address third-degree atrioventricular block seen on electrocardiography. The acetylcholine receptor (AChR) antibody was positive and anti-muscle-specific kinase (MuSK) antibody was negative. Despite these aggressive treatments, he had a sudden drop in blood pressure and died 4 days after admission.

Discussion

Pembrolizumab is an anti-programmed cell death protein 1 monoclonal antibody for the treatment of various cancers. Oncological outcomes and treatment-related AEs in patients with malignant tumors who received immune-checkpoint inhibitors were improved compared with those who were administered other anticancer agents. However, various irAEs have been reported that were sometimes fatal. There are 12 reports of pembrolizumab-related MG. In all cases, MG symptoms occurred relatively quickly after pembrolizumab administration. Although anti-AChR and anti-MuSK antibody are useful to diagnose MG, and especially to distinguish it from amyotrophic lateral sclerosis, not all cases diagnosed with pembrolizumab-related MG tested positive for anti-AChR and anti-MuSK antibodies. Several case reports described that steroid therapy should be administered in patients who have any abnormal neurological findings with or without serious symptoms. Wang et al. reported that if immune checkpoint inhibitor-related myocarditis is highly suspected, aggressive interventions, including intravenous methylprednisolone 1000 mg daily for 3 days followed by 1 mg/kg, should be promptly started, especially in fulminant cases.

The present case could not be confirmed by myocardial biopsy, because of chronic kidney disease. To our knowledge, this is the first reported case in which MG and myocarditis occurred as simultaneous pembrolizumab-related irAEs. Although these fatal irAEs are uncommon, it is important to select treatments considering fatal cases, such as the present case, before pembrolizumab administration. In addition, strengthening of collaboration of oncologists, immunologists, and specialists such as cardiologists and neurologists is necessary for a better treatment of irAEs.

Conclusion

We reported a case of MG and myocarditis in a patient with metastatic bladder cancer who had administered pembrolizumab. Clinicians using Pembrolizumab inhibitors should make treatment choices with MG and myocarditis in mind, and appropriate treatment should be given as soon as possible at onset.

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Declaration of competing interest

None.

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