Pembrolizumab-induced myasthenia gravis with myositis in a patient with lung cancer

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Keywords
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Abstract
In the new era of cancer immunotherapy, clinical research has uncovered diverse and unpredictable immune-related adverse events. Here, we report the first case of pembrolizumab-induced myasthenia gravis (MG) and myositis in a patient with lung cancer. The patient developed symptoms after the second infusion of pembrolizumab and was successfully treated with systemic corticosteroid therapy. With the accelerated development of immune checkpoint inhibitors as mono- or combination therapies for various malignancies, clinicians should closely monitor patients for important immune-related adverse events, such as MG, especially during the early phase of the treatment.

Introduction
In the new era of precision medicine, immune checkpoint inhibitors have dramatically changed the therapeutic approach to advanced and metastatic malignancies. Pembrolizumab, a humanized monoclonal antibody against programmed death 1 (PD-1), is approved for the treatment of various neoplasms. Immune checkpoint inhibitors exhibit marked therapeutic effects but are also associated with inflammatory side effects related to increased immune activity—immune-related adverse events (irAEs). Although rare, myasthenia gravis (MG) has been sporadically reported as a fatal irAE. Here, we report a case of MG with myositis after the second infusion of pembrolizumab in a patient with programmed cell death ligand 1 (PD-L1)-positive lung squamous cell carcinoma.

Case Report
An 83-year-old man was referred to our outpatient Department of Respiratory Medicine for a newly identified nodule in chest roentgenography. The patient was a lifelong non-smoker and had a past medical history of chronic stage 3 kidney disease and radical nephroureterectomy for low-grade urothelial carcinoma of the right ureter two years ago. Serological testing revealed elevated levels of cytokeratin19 (8.7 ng/mL; normal reference <3.5 ng/mL) and squamous cell carcinoma-related antigen (2.1 ng/mL; normal reference <1.5 ng/mL). Whole-body contrast-enhanced computed tomography (CT) revealed a pulmonary nodule of diameter 22 mm in the left lower lobe and lymphadenopathies in the mediastinum and abdominal para-aortic region. All lesions were strongly hypermetabolic in 18F-fluorodeoxyglucose positron emission tomography (PET) (Fig. 1A). The transbronchial biopsy and immunohistochemistry of the pulmonary nodule revealed well-differentiated squamous cell carcinoma with strong (80%–90%) positivity for PD-L1. Based on these findings, the patient was diagnosed with PD-L1-positive lung squamous cell carcinoma (cT1cN3M1c-StageIVB), and palliative immunotherapy with pembrolizumab (200 mg every three weeks) was immediately initiated.

On day 38 after the initiation of treatment (during the second cycle), the patient visited our outpatient clinic after experiencing narrowing visual field with diurnal fluctuation and easy fatigability of the eyelids and eye movement for a 10-day period, which decreased his Eastern
Cooperative Oncology Group—performance status (ECOG-PS) 2. Physical examination revealed bilateral ptosis; fissures in the right and left eyelids of size 3 and 6 mm, respectively (Fig. 2A); left side—restricted lateral eye movement; bilaterally restricted upward eye movement; diplopia; posterior neck myalgia; and neck extensor weakness (manual muscle test score of 4). Laboratory testing revealed elevated levels of serum creatine phosphokinase (CK) (4361 IU/L; normal reference <265 IU/L), aldolase (134.8 IU/L; normal reference <7.5 IU/L), myoglobin (4572.0 ng/mL; normal reference <60 ng/mL), lactate dehydrogenase (580 IU/L; normal reference <228 IU/L), aspartate aminotransferase (269 IU/L; normal reference <37 IU/L), and alanine aminotransferase (222 IU/L; normal reference <45 IU/L), indicating myositis and hepatitis. The patient tested negative for autoimmune antibodies related to MG, myositis, and hepatitis, including anti-acetylcholine receptor, anti-muscle specific kinase, anti-titin, anti-Kv1.4, anti-aminocarboxy tRNA synthetase, anti-melanoma differentiation-associated gene 5, anti-nuclear, anti-transcriptional intermediary factor-1 γ, anti-liver-kidney microsome 1, and anti-smooth muscle antibodies. The serological screening test results for viral hepatitis were also negative. Contrast-enhanced brain magnetic resonance imaging and abdominal CT did not reveal any metastases or morphological abnormalities. The results for high-frequency repetitive stimulation test were negative; however, the results of the eyelid fatigability, ice-pack (Fig. 2B), and edrophonium tests were positive. The patient was finally diagnosed with new-onset pembrolizumab-induced MG classified as IIA according to the Myasthenia Gravis Foundation of America clinical classification, with myositis and hepatitis based on the typical symptoms, examination findings, laboratory findings, timing of drug exposure, and exclusion of other possible causes.

The neurological symptoms remained unchanged after oral pyridostigmine treatment (60 mg, three times daily) for seven days. On day 45, the patient had an MG composite scale score of 12 and was started on oral prednisolone (20 mg, once daily). On day 51, the patient did not show any laboratory abnormalities and had an MG composite scale score of 4. Furthermore, CT and PET (Fig. 1B) performed on days 72 and 73, respectively, revealed a complete therapeutic response according to the Response Evaluation Criteria in Solid Tumors. On day 100, the patient showed ECOG-PS 0 with complete resolution of neurological symptoms (MG composite scale score of 0) and normal levels of serum tumour markers and muscle enzymes and was tapered off of prednisolone. The patient is currently being closely monitored in the outpatient clinic.

Figure 1. Frontal view of a fusion image of computed tomography and fluorodeoxyglucose positron emission tomography—computed tomography (FDG PET-CT). (A) FDG PET-CT performed prior to pembrolizumab treatment revealed hypermetabolic involvement in a pulmonary nodule in the left lower lobe and lymphoadenopathies in the mediastinum and abdominal para-aortic region (arrows). (B) FDG PET-CT performed on day 73 after two cycles of pembrolizumab showed physiological uptake and no hypermetabolic involvement.

Figure 2. Patient before (A) and after (B) the ice-pack test. (A) The patient had bilateral ptosis, and the palpebral fissure distances from the inferior margin of the eyelid to the superior eyelid margin over the pupil were 3 and 6 mm for the right and left eyes, respectively. (B) Three minutes after the placement of a cold pack over both eyes, ptosis was substantially diminished, and the palpebral fissure distances increased to 6 and 8 mm, respectively.
Discussion

Myasthenia gravis is diagnosed based on typical symptoms, the appearance of a neuromuscular junction disorder, and serum antibodies [1]. Anti-acetylcholine receptor antibody (anti-AChR) and anti-muscle-specific kinase antibody (anti-MuSK) have high specificity for MG [2]. Generally, anti-AChR and anti-MuSK are found in 80%–85% and 5%–10% of patients with idiopathic MG in Japan, respectively [3]. A recent report showed that 83% of nivolumab-related MG and 82% of idiopathic MG were positive for either anti-AChR or anti-MuSK [4]. Thus, false negative results are common; that is, a certain percent of double seronegative MG cases is irAEs or idiopathic. In the present case, MG was diagnosed in the absence of antibody positivity based on the typical symptoms and positive results of the eyelid fatigability, ice-pack, and edrophonium tests.

Nivolumab is also a humanized monoclonal antibody against PD-1, which was approved before pembrolizumab in Japan, and two years of post-market surveillance data of nivolumab use are available. Using these data, Suzuki et al. [3] described the clinical features of nivolumab-related MG as follows: an incidence of 0.12%; onset during the early phase after treatment initiation and rapid progression; high disease severity with a high frequency of myasthenic crisis; marked CK elevation associated with myositis or myocarditis; and good therapeutic responsiveness to immunosuppressive therapy. Thirteen sporadic cases of pembrolizumab-related MG have been reported in the literature, including the present case. Of these, nine cases were new-onset MG [5–11], and four cases were exacerbations of pre-existing MG [12–15]. Ten cases were of metastatic melanoma [5,7–9,11–15], and the remaining three cases were of thymic cancer [10], uterine carcinosarcoma [6], and lung squamous cell cancer (our case), respectively. Only five of these cases presented CPK elevation [4,6,9,10] (reported as 10,386 IU/L, 4361 IU/L [our case], 2125 IU/L, 1200 IU/L, and “slightly elevated”). All 13 patients developed MG soon after the initiation of pembrolizumab treatment. One patient developed fatal MG crisis that was aggressively treated with corticosteroids, pyridostigmine, intravenous immunoglobulin, and plasmapheresis; however, the patient ultimately died of acute respiratory failure 14 days after experiencing initial ocular symptoms and shortness of breath [9]. While it can be speculated that the clinical features of pembrolizumab-induced MG are similar to those of nivolumab-related MG, further studies are necessary to elucidate the exact features of pembrolizumab-induced MG.

In conclusion, we have described a case of seronegative MG with myositis that developed during the second course of pembrolizumab therapy as a first-line treatment for PD-L1-positive lung squamous cell carcinoma. The patient fully recovered from MG with systemic corticosteroid therapy, and lung cancer was completely resolved after only two courses of pembrolizumab therapy. To the best of our knowledge, this is the first reported case of pembrolizumab-induced MG in a patient with lung cancer. Clinicians should pay attention to the possibility of potentially fatal MG during the early phase of pembrolizumab treatment.

Disclosure Statement

Appropriate written informed consent was obtained for the publication of this case report and accompanying images.

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