Pembrolizumab induced bulbar myopathy and respiratory failure with necrotizing myositis of the diaphragm

Pembrolizumab, an anti-PD 1 antibody, has been approved for the treatment of metastatic melanoma [1, 2], non-small cell lung carcinoma [3, 4], and head and neck cancers [5]; and is being investigated in other cancers. We describe a case of Pembrolizumab induced severe bulbar myopathy and respiratory failure with necrotizing myositis of the diaphragm.

A 78-year-old man with BRAF wild-type metastatic melanoma with predominantly osseous metastases presented with a subacute onset of bulbar weakness 2 weeks after the second cycle of pembrolizumab. The week prior to admission, he had developed progressive dysarthria, bilateral ptosis, neck weakness, dysphagia, diffuse myalgia, and mild proximal muscle weakness in both the upper and lower extremities. He denied any fever, rash, dizziness or sensory deficit. At the time of admission, physical examination revealed asymmetric ptosis (Figure 1A), bifacial paresis (Figure 1B), mild ophthalmoparesis (pseudo-internuclear ophthalmoparesis—Figure 1C and D), flaccid dysarthria, mild neck flexion weakness, mild bilateral proximal limb muscle weakness (upper- > lower) and subtle facilitation. A PET-CT scan done at the time of hospitalization showed significantly decreased FDG uptake and size of all the osseous metastases. Initial laboratory testing revealed a mildly elevated WBC count at 16 000 and a mildly elevated creatine kinase (CK) at 1284 units per liter. Paraneoplastic antibody panel revealed a high titre of striational antibodies at 1:61 440, while anti-acetylcholine receptor antibody, anti-SRP70 (signal recognition particle), anti-HMGCR (3-hydroxy-3-methylglutaryl-coenzyme A reductase), and other paraneoplastic antibodies were negative. MRI of the cervical spine revealed symmetric enhancement of the paraspinal musculature. Electromyography showed reduced compound muscle action potential amplitudes in the spinal accessory and facial nerves without decrement or facilitation, contrary to the subtle facilitation on physical exam. Fibrillation potentials were noted in proximal muscle groups and in the orbicularis oculi muscles. These findings were consistent with ongoing muscle necrosis without evidence of a neuromuscular junction disorder. A triceps muscle biopsy showed necrotic fibers in most fascicles, replaced by mononuclear cells (Figure 2A). Taken together, the elevated CK, electromyography findings, laboratory studies, and the results of the muscle biopsy favored a diagnosis of an immune-mediated necrotizing myopathy over a NMJ disorder.

Prednisone was initiated at 1 mg/kg soon after the muscle biopsy was performed and he was discharged to the outpatient setting with prednisone the following day given stability of symptoms during the 3-day hospital stay. However, a week after discharge, he was readmitted with worsening bulbar myopathy and respiratory weakness. Despite the progressive weakness, his CK was normal, suggesting that the striational antibodies may have had a pathogenic role rather than a mere response to leaked myocytoplasmic antigens. He was initiated on PLEX (given two reports of its efficacy in immunotherapy associated necrotizing myopathy [6,7]) and underwent three sessions, but continued to

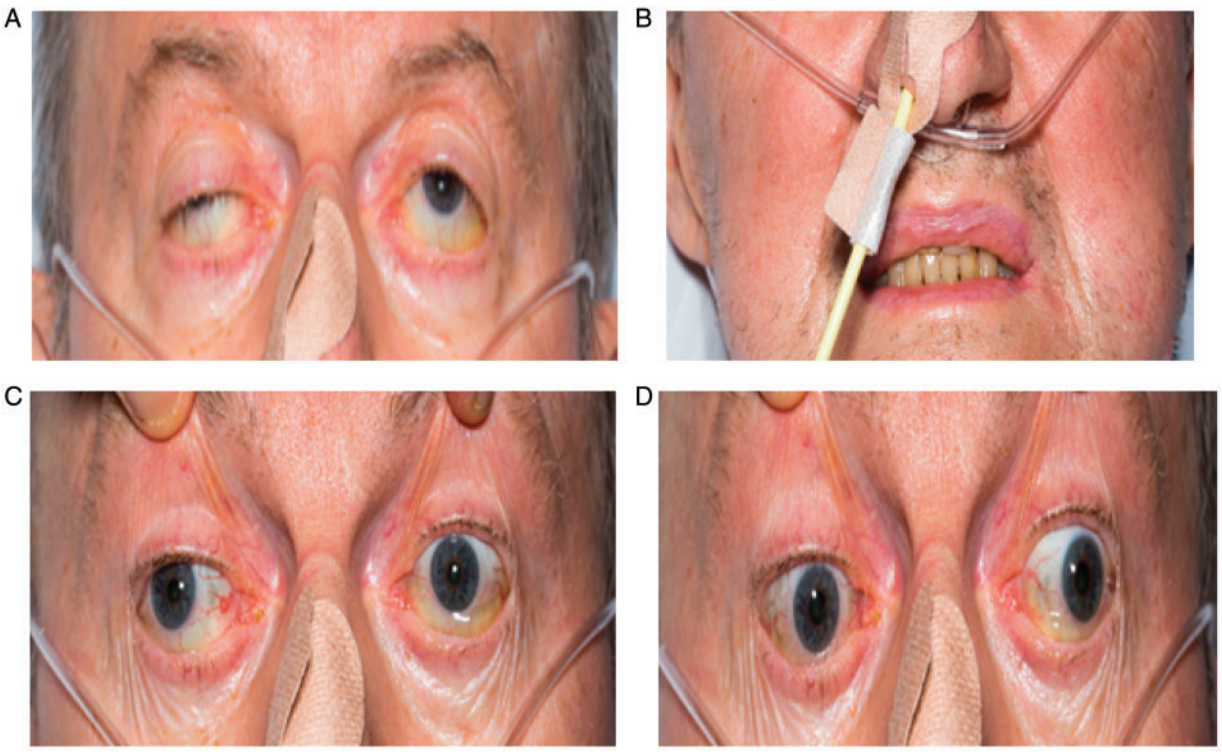

Figure 1. Neurologic examination demonstrating (A). Marked asymmetric ptosis (B). Bifacial palsy (C and D). Ophthalmoparesis (pseudo-internuclear ophthalmoplegia).

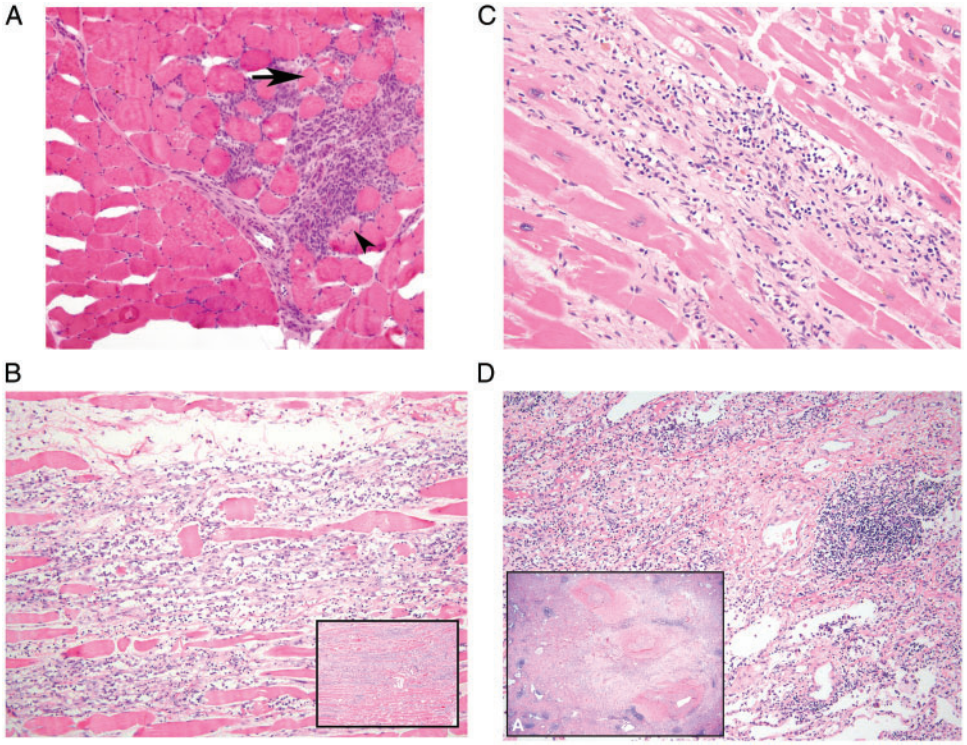

Figure 2. (A) Muscle biopsy showing a lymphohistiocytic infiltrate with muscle fiber necrosis (arrow) (H&E, 200×). (B) Active necrotic myositis involving the diaphragm with skeletal muscle loss and early fibrosis (H&E, 200×). Inset shows diffuse involvement at low magnification (H&E, 100×). (C) Patchy lymphohistiocytic myocarditis with moderate cardiac myocyte hypertrophy and interstitial fibrosis (H&E, 200×). (D) Histologic image of a prior metastatic site shows a nodular focus of fibrosis, lymphoid hyperplasia, with no viable metastatic tumor (inset A, H&E, 100×). Higher magnification of the periphery of the nodule reveals a lymphohistiocytic infiltrate composed of cytotoxic T-cells (as identified by immunohistochemistry) with adjacent alveolar lung parenchyma (H&E, 200×).

deteriorate. On hospital day 3, he was emergently intubated due to worsening respiratory weakness and mucous plugging leading to hypoxic respiratory failure. Amidst discussions of potential additional immunosuppressive therapy versus comfort care, the patient and his family requested terminal extubation given the severe deterioration and the underlying malignancy; and he passed away shortly thereafter. An autopsy was performed, which revealed diffuse necrotic myositis of the diaphragm (Figure 2B) and lymphohistiocytic myocarditis (Figure 2C). This was cited as the cause of death. No viable tumor was identified at the metastatic sites during the autopsy. These regions showed significant treatment effect, characterized by a predominantly cytotoxic T-cell population (Figure 2D).

This case highlights the importance of early diagnosis and recognition of the clinical course of necrotizing myopathy with immunotherapy. Given the fatal nature of this adverse effect and the potential to progress rapidly, we recommend close monitoring even in patients with a mild onset of symptoms and earlier aggressive up-titration of immunosuppression despite the theoretical risk of inhibiting the activity of anti-PD1 therapy against the underlying cancer. Pulse dose steroids, PLEX and IVIg could be initiated early and sequentially within a few days of refractoriness. In persistently refractory patients, proteasome inhibitors such as Bortezomib to deplete plasma cells and auto-antibodies, or calcineurin inhibitors to inhibit cytotoxic T cells may be a consideration. With the increasing use of immunotherapy in the treatment of cancer, this approach may significantly reduce morbidity and mortality from this fatal albeit rare adverse effect.

C. L. Haddox[1†], N. Shenoy[1†], K. K. Shah[2], J. C. Kao[3], S. Jain[1], T. R. Halfdanarson[1], E. F. Wijdicks[2] & M. P. Goetz[1*]
Departments of [1]Medical Oncology; [2]Anatomic/Clinical Pathology; [3] Neurology , Mayo Clinic, Rochester, USA
(*E-mail: goetz.matthew@mayo.edu)
[†]Both authors contributed equally as senior authors.

Acknowledgements

We acknowledge the contribution of Sean J. Pittock, Robert R. McWilliams, Elie Naddaf, Farwa Ali, Teerin Liewluck, Roberto A. Leon Ferre, Peter Lin, Joseph Maleszewski, Aimee Ripley and Jeffrey Winters.

Funding

None declared.

Disclosure

The authors have declared no conflicts of interest.

References

1. Robert C, Schachter J, Long GV et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015; 372: 2521–2532.
2. Robert C, Ribas A, Wolchok JD et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet 2014; 384: 1109–1117.
3. Garon EB, Rizvi NA, Hui R et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015; 372: 2018–2028.
4. Sul J, Blumenthal GM, Jiang X et al. FDA approval summary: pembrolizumab for the treatment of patients with metastatic non-small cell lung cancer whose tumors express programmed death-ligand 1. Oncologist 2016; 21: 643–650.
5. Chow LQ, Haddad R, Gupta S et al. Antitumor activity of pembrolizumab in biomarker-unselected patients with recurrent and/or metastatic head and neck squamous cell carcinoma: results from the phase Ib KEYNOTE-012 expansion cohort. J Clin Oncol 2016 Sep 19 [Epub ahead of print]; pii:JCO681473.
6. Zimmer SMG L, Hofmann L, Loquai C et al. Neurological, respiratory, musculoskeletal, cardiac andocular side-effects of anti-PD-1 therapy. Eur J Cancer 2016; 60: 210–225.
7. Vallet HGA, Weiss N, Vanhaecke C et al. Pembrolizumab-induced necrotic myositis in a patient with metastatic melanoma. Ann Oncol 2016; 27: 1352–1353.

doi:10.1093/annonc/mdw655
Published online 19 December 2016