Pembrolizumab induced refractory ocular myasthenia gravis: A case report

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Abstract
Immune checkpoint inhibition is a new and promising therapy approved for the treatment of various malignancies. Pembrolizumab is a potent tumour suppressor that acts by upregulating the immune system to recognise cancer cells, which may result in disrupted self-tolerance. We describe a case of seronegative ocular myasthenia gravis after treatment with pembrolizumab for metastatic melanoma. Her bilateral ptosis was refractory to conventional treatment, and she remains functionally blind as a result. As the availability and use of immunotherapy continues to rise, awareness of its immune-related adverse effects (irAEs) is crucial for clinicians.

Introduction
Precision medicine has radically changed the treatment landscape of advanced malignancies. Pembrolizumab is an immune checkpoint inhibitor with potent therapeutic effects against tumour cells that express programmed cell death 1 ligand (PD-L1).1 Approved for multiple neoplasms, these monoclonal antibodies bind to PD-L1 and inhibit the downregulation of T cells, allowing tumour suppression through immune system activation.2 However, disrupted self-tolerance can lead to rare and serious immune-related adverse effects (irAEs), including myasthenia gravis, autoimmune encephalitis, myocarditis, peripheral neuropathies and inflammatory myopathies.1 Here, we describe a case of seronegative ocular myasthenia gravis after treatment with pembrolizumab for metastatic melanoma.

Case report
We report a case of a 77-year-old Caucasian woman with metastatic melanoma with mediastinal lymphadenopathy and lung involvement. Her medical history of note included pT1N0 low grade rectal adenocarcinoma resected a decade prior, type 2 diabetes mellitus, and atrial fibrillation (on rivaroxaban 15 mg). When commenced on pembrolizumab three times a day, with no effect. Intravenous immunoglobulin (IVIG) and plasmapheresis were attempted, with no treatment benefit. The neurologist’s opinion remained that myasthenia gravis was the most likely diagnosis, despite symptoms being refractory to treatment. Though all conventional management strategies have been exhausted, our patient remains functionally blind due to near-complete bilateral ptosis. Despite her CT showing marked reduction in her mediastinal lymphadenopathy and lung metastases, the difficult decision to discontinue her pembrolizumab had to be made. Oculoplastic surgical intervention was the only option remaining as end-of-line treatment for her bilateral ptosis.

Discussion
While immunotherapy has advanced the treatment options for various malignancies, more needs to be understood regarding their associated immune-related adverse events (irAEs).3 Pembrolizumab-induced myasthenia gravis appears to be a rare but well described phenomenon with varying prognosis. Gutierrez et al.1 reported that to date, there are only ten reported cases, three of which are exacerbations and three are de novo. The clinical course and severity of symptoms appear to be variable, with some reported fatal outcomes secondary to myasthenic crisis.3 These irAEs are not limited to pembrolizumab or the nervous system, as case reports of other anti-PD-1L therapies like nivolumab and ipilimumab describe similar neurological, respiratory, muscularkeletal, cardiac, ocular, and haematopoietic adverse events.3 Zimmer et al.4 found that neurological side effects often persisted despite treatment, with sequelae such as paresis and multifocal central nervous system demyelination. Their systematic review described multiple neurological syndromes associated with immune checkpoint inhibition, including Tolosa-Hunt syndrome, a seronegative cause of painful ophthalmoplegia, and Guillain-Barré syndrome, an acute demyelinating disorder with ocular manifestations.4 Overlap syndromes are well documented for immune-related myasthenia gravis (irMG).
Concurrent myocarditis and/or myositis can manifest with irMG and is often a predictor of poor outcome.5

Our case appears to have isolated ocular myasthenia gravis with no significant systemic or respiratory involvement. Seronegative myasthenia gravis appears to occur more commonly in ocular than generalised presentations, with acetylcholine receptor antibodies detected in less than half of new-onset myasthenia gravis secondary to anti-PD1L therapy.2,6 Myasthenia gravis is a known paraneoplastic syndrome of malignant thymoma, where an abnormal immune response towards cancer cells results in antibodies that mistakenly attack the nervous system.1 Thymoma was investigated and excluded in our case through computed tomography, and evidence for other neoplasms causing paraneoplastic myasthenia gravis are lacking.1 Therefore a paraneoplastic antibody screen was not performed. It is not uncommon for immune-related myasthenia gravis to be seronegative and refractory to treatment.1 Other literature reviews like Gonzalez et al.3 have recommended steroids, infliximab, IVIG, and plasma exchange as treatment, which our case mostly received, while typically avoiding immunosuppressive medications. Many case reports describe the discontinuation of cancer immunotherapy upon development of adverse events, and the decision to re-challenge or continue treatment remains a difficult one, especially for those with a positive cancer response.3

Conclusion
In conclusion, we describe a case of seronegative ocular myasthenia gravis that developed during the second course of pembrolizumab therapy for her metastatic melanoma. Her bilateral ptosis was refractory to conventional immunotherapy, and she remains functionally blind as a result. This case highlights the need for a high index of suspicion when patients on checkpoint inhibitors develop ocular symptomatology, as their use continues to increase.

References

About the authors

Chaolan (CC) Zheng is a Trainee intern from the University of Otago, Wellington and had chosen her elective placement in Neurology. She received the 2020 Fowler Scholarship for her campus and is incredibly passionate about ongoing learning and human connection through all life stages.

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Acknowledgements
The authors would like to acknowledge the Neurology Department at Wellington Hospital and the General Medicine Department at Hutt Hospital for their support with this work.