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Review

Myasthenia gravis: An emerging toxicity of immune checkpoint inhibitors

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Abstract The advent of immunotherapy has heralded a number of significant advances in the treatment of particular malignancies associated with poor prognosis (melanoma, non-small-cell lung, renal and head/neck cancers). The success witnessed with therapeutic agents targeting cytotoxic T-lymphocyte-associated protein 4, programmed cell death protein 1 and programmed cell death ligand 1 immune checkpoints has inevitably led to an explosion in their clinical application and the subsequent recognition of specific toxicity profiles distinct from those long recognised with chemotherapy. Consequently, as the utility of such therapies broaden, understanding the nature, timing and management of these immune-related adverse events (irAEs) becomes increasingly significant. Although neurological irAEs are considered relatively rare in comparison with hepatitis, colitis, pneumonitis and endocrinopathies, one emerging side-effect is myasthenia gravis (MG). Among the 23 reported cases of immune checkpoint inhibitor-associated MG, 72.7% were *de novo* presentations, 18.2% were exacerbations of pre-existing MG and 9.1% were exacerbations of subclinical MG. The average onset of symptoms was within 6 weeks (range 2–12 weeks) of treatment initiation. In addition, there was no consistent association with elevated acetylcholine antibody titres and the development of immune checkpoint inhibitor-related MG. Significantly, there was a 30.4% MG-specific-related mortality, which further emphasises the importance of early recognition and robust treatment of this toxicity. In addition to a review of the existing literature, we present a new case of pembrolizumab-induced MG and provide insights into the underlying mechanisms of action of this phenomenon.

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1. Introduction

Over the past 5 years, targeted immunotherapy has created a major paradigm shift within the therapeutic landscape of numerous solid tumours. Manipulation of pathways which mediate blunting of anti-tumour immunity has predominantly focussed on the development of inhibitors directed against the immune checkpoint modulators such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1) and its ligand, PD-L1. The introduction of these novel agents has not only witnessed unprecedented extensions in survival outcomes for patients with malignant melanoma, lung, renal and head/neck cancers but reveals a plethora of immune-related toxicities for which early recognition and appropriate clinical management are paramount. Autoimmune events including hepatitis, colitis, pneumonitis, dermatitis, nephritis, endocrinopathies and hypophysitis are well-recognised phenomena which represent a manifestation of dysregulated inflammation induced by immune checkpoint inhibition. As the use of these targeted agents expand, further toxicity issues have emerged. Recently, this has been exemplified by both *de novo* presentations and exacerbations of pre-existing myasthenia gravis (MG) which, to date, has been reported in 22 cases in the literature. Herein, we present a new presentation of ocular MG (oMG) followed by a succinct review of cases highlighting this phenomenon.

2. *De novo* myasthenia gravis

2.1. Case report

An 85-year-old woman with metastatic melanoma with left axillary lymphadenopathy commenced single-agent pembrolizumab (2 mg/kg; every 3 weeks) and tolerated the first cycle without any significant toxicity. Shortly after the second cycle, she presented with diplopia that was subsequently followed by asymmetrical bilateral ptosis (L > R). The remaining neurological examination was unremarkable, and there was no evidence of oesophageal dysmotility or respiratory compromise. Brain magnetic resonance imaging (MRI) confirmed no evidence of metastatic dissemination, and both acetylcholine receptor antibodies (AChR-Abs) and anti-muscle-specific kinase antibodies (anti-MuSK Abs) were normal. In view of the high clinical suspicion of oMG, she commenced systemic treatment with intravenous immunoglobulin (IVIG; 30 g/300 mL daily for 5 d), prednisone (100 mg once daily (o.d.) for 7 d) and pyridostigmine (90 mg daily). This regimen elicited a swift clinical response with complete resolution of bilateral ptosis and diplopia. She continued a maintenance schedule of monthly IVIG and daily oral pyridostigmine without any further symptomatic recurrence. In view of the *de novo* presentation of oMG, pembrolizumab was discontinued, and the patient passed away shortly afterwards from unrelated cardiac issues.

3. Anti-PD-1 inhibitor-induced myasthenia gravis

In addition to this aforementioned report, since the introduction of PD-1 and PD-L1 immune checkpoint inhibitors, there have been several publications highlighting a causal relationship with the manifestation of *de novo* MG (Table 1).

Indeed, March *et al.* [1] recently documented a fatal case in a 63-year-old male with malignant melanoma of the right scalp, which had metastasised to the liver and brain, who was also treated with pembrolizumab. Two weeks after the first cycle, he presented with right ptosis, facial oedema, diplopia and dyspnoea on mild exertion. Brain MRI confirmed early response within the pre-existing brain metastases, positive AChR-Abs and negative anti-MuSK Abs. Two days after the hospitalisation, he developed progressive facial weakness, bilateral ptosis and increasing dyspnoea. Unfortunately, the presentation was refractory to appropriate intervention with pyridostigmine, high-dose steroids, IVIG and plasmaphaeresis, and he subsequently passed away from ventilatory failure.

Although the majority of *de novo* cases of MG warranted comprehensive clinical management, a select group of patients responded with comparatively minimal intervention. Gonzalez *et al.* [2] documented a case of a 71-year-old woman with refractory metastatic uterine carcinosarcoma who developed dysphagia, diplopia and dysarthria after four cycles of pembrolizumab. Three weeks post symptomatic onset, she developed left lateral rectus weakness, with further diplopia and ptosis (R > L). This progressed to neck extensor and proximal upper and lower limb weakness. Creatinine kinase (CK) was significantly elevated (1200 IU/l), and serology was negative for both AChR-Abs and anti-MuSK Abs. Subsequent treatment with 50-mg pyridostigmine three times daily (t.d.s.) and prednisone 20 mg o.d. alone led to a complete symptomatic response over the following 3 weeks [2]. Similarly, Nguyen *et al.* [3] reported two cases in patients with metastatic melanoma treated with pembrolizumab whereby minimal rescue therapy (i.e. without IVIG or plasmaphaeresis) resulted in a full resolution of the myasthenic symptoms. The first report highlighted a male patient who developed bilateral ptosis 5 d before the fourth cycle. Interestingly, 25-mg daily prednisone induced complete amelioration of symptoms without any delay in treatment. The second case documents a female who developed bilateral ptosis and dysphagia 7 weeks post initiation of pembrolizumab. She achieved a significant response after 10 d of the steroid therapy consisting of methylprednisolone 500 mg intravenous (i.v.) for 5 d followed by oral prednisolone slowly tapered over 4 weeks [3].