Myasthenia gravis and concurrent myositis following PD-L1 checkpoint inhibitor for non-small cell lung cancer

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ABSTRACT
Background There are increasing reports of myasthenia gravis (MG) following oncological treatment with immune checkpoint inhibitors (ICIs).
Methods and results A 66-year-old man with stage 3A lung adenocarcinoma was treated with second weekly infusions of durvalumab, a programmed cell death ligand-1 inhibitor, at a dose of 10 mg/kg. After the fourth infusion, he developed diplopia, dyspnoea and constitutional symptoms including headache, weakness and anorexia. 1 month later, he developed dysphagia and dysphonia. Examination showed proximal limb weakness with fatigability. An ice pack test was positive. Blood tests revealed a raised creatine kinase and positive PM-Scl75 antibody. Antititin antibody was strongly positive in the serum and cerebrospinal fluid. Antibodies for acetylcholinesterase receptor and antimuscle-specific kinase were negative. Electromyography showed myopathic changes. The patient was treated with steroids, mycophenolate mofetil and intravenous immunoglobulin. Eight weeks after treatment initiation ptosis, eye movements and limb strength were markedly improved and repeat creatine kinase was normal.
Conclusion Clinicians using ICIs should have a high index of suspicion for ICI-induced MG and concurrent myositis as disease can be severe and is associated with high mortality rates.

INTRODUCTION
Immune checkpoint inhibitors (ICIs) are monoclonal antibodies which modulate immune-regulatory mechanisms to induce an antitumour response. In recent years, ICIs are increasingly being used in the field of oncology to treat various cancers with encouraging results. While it is a novel approach to use the body’s immune system to fight cancer, such a strategy has led to the emergence of various autoimmune-related toxicities. Neurological immune-related adverse events include encephalitis, aseptic meningitis, transverse myelitis, Guillain-Barré syndrome, peripheral neuropathy, myositis and neuromuscular junction disorders including Lambert-Eaton myasthenic syndrome and myasthenia gravis (MG).

Durvalumab is a fully humanised immunoglobulin monoclonal antibody that blocks the interaction of the programmed cell death ligand-1 (PD-L1) with the programmed cell death receptor-1 (PD-1) and CD80, which is one of the immune escape mechanisms of tumour cells. MG, an autoimmune disorder of neuromuscular junction, has been reported in association with several ICIs including atezolizumab, pembrolizumab, nivolumab and ipilimumab.

Over one-third of ICI-associated patients with MG may have a concurrent myositis and myocarditis may also occur. In addition ICI-associated myositis may rarely present with limited involvement to the facial and extraocular muscles and even mimic MG. We present a case of a 66-year-old man who developed concurrent antititin antibody positive generalised MG and PM-Scl75 positive myositis following treatment of non-small cell lung cancer with the PD-L1 inhibitor, durvalumab.

CASE REPORT
A 66-year-old man was diagnosed with stage 3A adenocarcinoma of the right lung. He was treated with two cycles of cisplatin and etoposide, followed by 6 weeks of radiotherapy at a dose of 60 Grays to the right lung and mediastinum. Approximately 1 month after radiotherapy was completed, he commenced second weekly infusions of durvalumab, a PD-L1 inhibitor, at a dose of 10 mg/kg.

The first three infusions of durvalumab were uneventful. One week after the fourth infusion, the patient noticed a mild right ptosis. Three days after the fifth infusion, he developed diplopia, dyspnoea and constitutional symptoms including headache, weakness and anorexia. Amonth later, he developed dysphagia, dysphonia and limb weakness.
On examination, there was right ptosis and restricted extraocular eye movements in all directions except downward gaze. An ice pack test was positive. There was mild proximal limb weakness with fatigability.

Blood tests revealed a mildly raised creatine kinase (CK) 499 U/L and positive PM-Scl75 antibody. Antibodies for acetylcholinesterase receptor (anti-AChR), antimuscle-specific kinase (anti-MuSK), antivoltage-gated potassium channel and antivoltage-gated calcium channel were negative on two separate occasions. Antiangioidide antibodies to GQ1b, GM1, GT1b, GD1a, GM2 and GM3 were also negative. Serum and cerebrospinal fluid (CSF) antineuronal antibody testing were strongly positive for anti-titin antibodies. Other CSF findings included a normal protein count 0.39 g/L and no cells. MRI brain and orbits was normal. CT chest, abdomen, pelvis was normal.

The findings of ptosis, extraocular muscle weakness, dysphagia, limb fatigability, supportive ice pack test and cardiogram was normal. Electromyography showed mild myopathic changes. Repetitive stimulation showed no decrement or facilitation. Transthoracic echocardiogram was normal.

The findings of ptosis, extraocular muscle weakness, dysphagia, limb fatigability, supportive ice pack test and positive anti-titin antibodies were considered diagnostic of MG. The patient’s systemic features, proximal limb weakness, raised CK, positive PM-Scl75 antibody and myopathic electromyography led to a concurrent diagnosis of myositis. Treatment for ICI-induced MG and myositis with prednisone 60 mg daily and pyridostigmine titrated to 120 mg three times a day was commenced. Two weeks later, he showed mild improvement in ptosis and eye movements, and dysphagia had resolved. Intravenous immunoglobulin induction 2 g/kg was given with further improvement. At the 4 weeks mark, the patient had further improvement in symptoms. Mycophenolate mofetil 1 g two times per day was commenced and prednisone weaned. Eight weeks after treatment initiation ptosis, eye movements and limb strength were markedly improved and repeat CK was normal.

The patient and his oncologist decided to cease durvalumab.

DISCUSSION
There are increasing reports of fulminant autoimmune toxicity following ICI treatment. Neurological adverse events are reported in around 6% of patients treated with ICIs with exacerbations of pre-existing and de novo presentations of MG the most commonly reported association in 0.12%–0.2%. Muscle disorders are the second most common association in 0.58%–0.76%. A concurrent diagnosis of ICI-induced MG and myositis has been reported in 37% and myocarditis in 8% of a large series of patients with ICI-induced MG. ICI-induced MG usually occurs within the first to fifth infusion. While many cases of MG have been associated with PD-1 and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitors, our case was induced by a PD-L1 inhibitor. Previous cases of ICI-induced MG are reported with combination durvalumab and tremelimunab, and durvalumab and nivolumab therapy. Our case directly implicates the single agent durvalumab as the cause of MG and myositis.

Negative anti-AChR and anti-MuSK antibodies and positive antititin antibodies, as in our case, are previously described findings in ICI-induced patients with MG. Elevation of CK and positive myositis antibodies including PM-Scl75 antibody are also recognised associations. ICI-induced myositis has been documented to affect orbital and facial muscles and mimic myasthenia including in a recently reported patient with positive PM-Scl75 antibody. Muscle biopsies performed in some cases show varying pathologies including necrotising myopathy, non-specific myopathy and dermatomyositis findings. ICI-induced MG and myositis is reported to respond to steroids, acetylcholine esterase inhibitors, intravenous immunoglobulin or plasmapheresis, and other immunomodulatory therapies. Reports suggest patients treated with intravenous immunoglobulin or plasmapheresis (regardless of steroid) as first-line treatment have better outcomes. Our patient improved with pyridostigmine and immunomodulation with normalisation of CK, confirming efficacy of standard treatment regimens and suggesting that CK levels may reflect treatment response. The severity of MG in our patient was moderate, but mortality rates of 30% in ICI-induced MG are reported.

Recommendations vary regarding as to whether ICIs should be discontinued after diagnosis of ICI-induced MG. In the largest series of patients with ICI-induced MG, the ICI was discontinued in most (97%) and readministration was reported for six patients after stabilisation of MG symptoms. All of these patients were maintained on prednisone, pyridostigmine and/or intravenous immunoglobulin at the time of ICI readministration. The literature suggests that readministration of ICIs can be considered in patients with mild to moderate neuromuscular symptoms once side effects have resolved. However, reports indicate that in patients with severe side effects, especially those involving the heart, ICI reintroduction can potentially be fatal.

CONCLUSION
The increasing use of ICIs requires neurologists, and medical oncologists to promptly recognise the full spectrum of neurological immune-related adverse events including MG, myositis and limited ocular myositis. MG induced by ICIs can be severe, may be associated with concurrent myositis or myocarditis and is associated with high mortality rates. Early recognition and prompt standard treatment will likely reduce mortality and morbidity.

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