Case report

A rare case of Miller Fisher variant of Guillain-Barré Syndrome (GBS) induced by a checkpoint inhibitor

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SUMMARY

With the recent development of novel, more potent cancer treatment, in particular, immune 'checkpoint inhibitors', cases of neurological immune-related adverse events are on the rise. Although rare, this includes Guillain-Barré Syndrome (GBS). We present the case of a 68-year-old male who was admitted with sudden onset of worsening neurological symptoms following immunotherapy treatment. These symptoms progressed quickly to respiratory failure requiring intubation and admission to the intensive care unit. He was thoroughly investigated and is believed to have an axonal neuropathy in the form of Miller Fisher Syndrome (MFS) variant of GBS, secondary to immunotherapy treatment. He was initially treated with intravenous immunoglobulin, and later, perhaps more effectively, with high dose steroids which significantly improved his symptoms. This case of checkpoint inhibitor-induced MFS is one of few in the literature and is an important reminder of the potential for new immunotherapeutic agents to cause significant neurotoxic effects. These should be promptly and thoroughly investigated, in particular, as the management of these patients can differ from standard treatments used in these conditions.

BACKGROUND

Nivolumab is a type of targeted immunotherapy used to treat patients with unresectable tumours. It is a fully human IgG4 monoclonal antibody, which acts by blocking an inhibitory receptor on T-cells called programmed death-1 (PD-1). By blocking PD-1, it promotes T-cell activation leading to increased immune response and decreased tumour growth. It is currently used as first-line treatment for metastatic melanoma and second-line treatment for both squamous cell lung cancer and renal cell carcinoma (RCC).[1 2]

The most common immune-related adverse events (irAEs) affect the gastrointestinal and dermatological systems,[3] but endocrine, pulmonary and neurological adverse events are also reported, the latter reported least frequently. Their severity ranges from mild (grade 1) to fatal (grade 5).[4 5] Grade 4 irAEs represent life-threatening events, as in our case. Their time of onset can vary with some cases starting after the first cycle, while others occur months to years later.[6]

While the true prevalence of such irAEs is unknown, neurological complications may complicate up to 1% of cases.[6] Given the rise in the use of immunotherapy drugs and positive impact on mortality, such complications are likely to be more frequent presentations to secondary care physicians and neurologists.

The most commonly documented neurotoxicity is a peripheral polyneuropathy, followed by myositis and a neuromuscular junction disorder, such as myasthenia gravis.[7] Cases of irAEs causing the Miller Fisher variant of Guillain-Barré Syndrome (GBS), however, are rare. There is only one reported case of immunotherapy toxicity in the form of Miller Fisher variant of GBS.[8] The case presents a patient being treated with ipilimumab and nivolumab for metastatic melanoma. The patient presented similarly to this case with progressive ataxia, diplopia and ptosis 10 days after immunotherapy. Initial treatment compromised intravenous immunoglobulin and intravenous methylprednisolone. This was followed by plasmapheresis and maintenance oral prednisolone and immunoglobulin infusions, and the patients' symptoms improved significantly.

A 2017 paper reviewed five reported cases of GBS secondary to immunotherapy. They concluded that all patients had been treated with a regime of intravenous immunoglobulin or other immunotherapy. Of these five cases, 40% improved, 20% did not improve and 40% died due to respiratory insufficiency and multiorgan failure.[9] The devastating, potentially fatal but treatable consequences of severe neurotoxicity means their prompt recognition is essential.

CASE PRESENTATION

A 68-year-old independent and physically active retired military serviceman presented in February 2018 to the emergency department with progressive symptoms of weakness and sensory disturbance in his face and limbs over 10 days. He initially noticed a left facial droop involving the forehead, diagnosed as a Bell's Palsy and treated with steroids and acyclovir. This progressed within days to slurred speech, double vision, difficulty swallowing, shortness of breath, paraesthesia of his hands and feet, an unsteady gait and general weakness.

Apart from type 2 diabetes mellitus and hypertension, his most notable past medical history included RCC with multiple organ metastases, for which he had received intravenous infusions of immunotherapy agent, nivolumab. He was diagnosed 2.5 years prior to neurological presentation, at which point he underwent a radical nephrectomy. Following the detection of pancreatic, lung, adrenal and bone metastases, he had an ulnar bone resection and fixation for symptomatic relief and

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was started on treatment with vascular endothelial growth factor inhibitor pazopanib for a total of 2 months. This was followed by four intravenous infusions of nivolumab at a dose of 240 mg (3 mg/kg) every 2 weeks. The last infusion was 4 days prior to his admission to hospital.

Initial neurological examination revealed near-complete ophthalmoplegia, reduced upgaze, a left facial palsy including the forehead and dysarthric speech with no clear evidence of fatiguability. In the left upper limb, weakness consistent with an ulnar neuropathy was noted secondary to surgery mentioned above, but otherwise had normal tone, power and deep tendon reflexes. His gait was ataxic. General examination was otherwise unremarkable.

Within 72 hours, he developed rapidly worsening bulbar symptoms, and despite 3 days of treatment with intravenous immunoglobulin (IVIg) developed severe global limb weakness and respiratory decompensation. On the intensive care unit (ICU), he was later noted to have a tetraparesis with global areflexia with relatively preserved sensation. Cranially, he had bilateral asymmetrical ptosis, bilateral complex ophthalmoplegia, anarthria and bifacial paresis with incomplete eye closure.

INVESTIGATIONS

On admission, routine blood tests, including inflammatory markers, ECG and chest radiograph, were normal. A non-contrast CT and MRI scan of the brain and cervical spine were within normal limits, and a CT scan of the abdomen appeared stable. A lumbar puncture, performed 2 weeks after symptoms onset, revealed cytoalbuminologic dissociation (protein 1.75 g/L, five lymphocytes), with otherwise normal constituents, including cytology.

Acetylcholine receptor antibodies and antiganglioside antibodies were reported negative after 2 weeks. Neurophysiological testing, available only 10 days after admission, included nerve conduction studies, single-fibre electromyography (EMG; including orbicularis oculi) and repetitive nerve stimulation, which were within normal limits, but when repeated weeks later, did suggest the probability of Miller Fisher variant of GBS. Specifically, the nerve conduction studies revealed that although peripheral sensory responses were preserved in the lower limbs, motor function was markedly reduced. Peroneal and tibial motor responses were reduced in amplitudes with slowed motor conduction. Median motor responses were lower in amplitude on the right with prolonged distal motor latency and mildly slowed conduction velocity. Ulnar motor conduction also showed lower amplitude motor responses with slightly slowed conduction velocity. The right tibial and ulnar F wave responses were unrecordable. Needle EMG also showed acute denervation potentials in most of the sampled facial muscles including left mentalis.

DIFFERENTIAL DIAGNOSIS

Initial differential diagnoses were broad, but after exclusion of central nervous system pathology, including neoplastic or granulomatous infiltration or infection, the most likely peripheral neurological causes included an acute inflammatory neuropathy, such as GBS, or a neuromuscular junction disorder, such as Myasthenia Gravis. Given the rapid onset of bulbar symptoms, respiratory dysfunction, ophthalmoplegia and facial paresis, a clinical diagnosis of Miller Fisher variant of GBS was favoured over a neuromuscular disorder. The close temporal relationship between treatment with nivolumab and symptom onset, as well as the lack of any preceding infection, suggested his presentation was most likely secondary to the checkpoint inhibitor, in line with previous literature suggesting the link.

TREATMENT

At the onset of deterioration in bulbar function, he was commenced on a 5-day course of IVIg (2 g/kg total) for a presumptive diagnosis of a neuromuscular junction or peripheral nerve disorder. Despite 3 days of treatment, he developed severe global limb weakness and respiratory decompensation, necessitating intubation and ventilation on the ICU. At this point, he was commenced on intravenous methylprednisolone (3 mg/kg/day) followed by oral prednisolone 100 mg daily in addition to pyridostigmine. The latter was discontinued after EMG excluded a neuromuscular junction disorder, and his prednisolone was weaned over a period of months.

OUTCOME AND FOLLOW-UP

At best, a modest response to initial IVIg therapy was observed. Subsequent treatment with high-dose corticosteroid allowed improvements in respiratory function, motor weakness and extubation at 9 days. He was subsequently transferred to the specialist cancer ward and thereafter to the regional neurorehabilitation unit.

Three months after his initial presentation, cranial examination was normal. His power was 4 to 4+/5 in the upper limbs (4 on the left and 4+ on the right), with some similar pattern in the lower limbs but absent knee jerks and ankle jerks and flexor plantars. He was discharged back home with input from a community rehabilitation team for 6 weeks postdischarge. He was reviewed by the neurology at this time, who recommenced steroids at 40 mg alternative days. He was subsequently reduced to 35 mg alternate days for a month and thereafter to stay on 30 mg alternate days.

DISCUSSION

There is a wide range of adverse neurological adverse effects related to immune-checkpoint inhibitors. These include disorders of the central nervous system such as acute cerebellitis,[10] encephalitis,[11] meningitis,[12] transverse myelitis[13] and peripheral nervous system such as facial nerve palsies,[14 15] chronic immune demyelinating polyneuropathy,[13] GBS[12 16–18] and myasthenia gravis.[19–22]

Miller Fisher is characterised by a triad of ophthalmoplegia, ataxia and areflexia. Additional symptoms, like in this case, may include generalised muscle weakness and respiratory failure.[23] We conclude that this patient had a severe irAEs manifesting as Miller Fisher subtype of GBS. Given the timing of the presentation, 4 days after therapy with nivolumab, plus the rising association of neurotoxicity and immunotherapy in literature, an irAE is the most likely cause.

We would measure this adverse event as a Grade 4 'life-threatening' event due to respiratory failure requiring intubation and ventilation on the ICU.

This case showed the clinical features of GBS, and the presence of ataxia, areflexia and ophthalmoplegia suggest Miller Fisher syndrome (MFS). In this case, the antiganglioside antibody testing including anti-GQ1b was negative. The anti-GQ1b test has been shown to be positive in approximately 85% of cases of MFS.[24] In both the case presented here and the previously documented case, these antibodies were negative. It is important to consider a neurological irAE and more specifically MFS even if this test is negative. More work is needed to further define the optimum time after onset of symptoms to test for anti-GQ1b.

The most dramatic improvement in this patient was seen after the introduction of high-dose steroids, which significantly improved his symptoms. In the only other published case of immunotherapy-related MFS, the patient was treated similarly with a combination of IVIg and intravenous methylprednisolone, followed by plasmapheresis and maintenance oral steroids and IVIg infusions. This combination treatment also produced significant improvement in symptoms.

There have been multiple cases of fatality due to irAEs.[17] Given the significant morbidity and mortality associated, it is important to recognise diagnosis and promptly treat all variants of neurological toxicity.

Learning points

- Neurological toxicity can occur soon after initial administration or as a delayed presentation up to 2 years after immune checkpoint inhibitor therapy.
- As use of such drugs increase, neurological toxicity is likely to become a more common encounter in secondary care.
- The risks of such side effects should be explained to patients prior to treatment.
- There is relatively little evidence to guide treatment, but early use of high-dose steroid therapy can provide a significant improvement in symptoms and may be more effective than intravenous immunoglobulin.

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