Miller Fisher Syndrome Associated With Immunotherapy for Metastatic Melanoma

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Abstract

Immunotherapy is a treatment strategy that has demonstrated survival benefit for metastatic melanoma. Ipilimumab and nivolumab are examples of immunotherapy, in which monoclonal antibodies antagonize cytotoxic T-lymphocyte-associated protein 4 and programmed death-ligand 1 receptors, respectively, resulting in upregulation of the host immune response to cancer cells. There is increasing recognition of immune-mediated adverse events associated with immune therapies in patients with cancer. We present a case report of a patient who developed Miller Fisher syndrome associated with these therapies for metastatic melanoma along with a discussion of its management.

Keywords

Miller-Fisher syndrome, immunotherapy, melanoma, CTLA-4 receptor, PD-1 receptor

Introduction

Ipilimumab and nivolumab are monoclonal antibodies that bind to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death-ligand 1 (PD-1) receptors, respectively, preventing their activation. These T lymphocyte receptors regulate immune tolerance to self-antigens. Antagonism of CTLA-4 and PD-1 receptors is a developing area of immunotherapy that enhances the host immune response to cancer cells. This approach is associated with toxicities such as colitis, rashes, hepatitis, endocrinopathies, and pneumonitis¹⁻³; however, neurological immune-mediated adverse events are increasingly recognized. We report the first case of Miller Fisher syndrome (MFS) associated with ipilimumab and nivolumab combination therapy in metastatic melanoma.

Case Description

A 58-year-old woman, with a history of treated hypothyroidism, presented with progressive ataxia, diplopia, and ptosis evolving over 1 week, associated with perioral and hand paresthesia. She presented to hospital 10 days post cycle 1 of ipilimumab and nivolumab therapy for BRAF-positive stage IV metastatic melanoma. The patient had been recently diagnosed with melanoma following investigation for sciatic-type back pain with weight loss, due to sacral and liver metastases. As part of a clinical trial, she had received concurrent

radiotherapy to the sacral metastasis. There was no recent infective illness, vaccinations, or surgery prior to presentation.

Initial examination revealed bilateral ptosis and external ophthalmoplegia, characterized by limitation of eye movements in all directions with partial sparing of eye depression and absence of pupillary involvement. Marked truncal and limb ataxia were also evident accompanied by impaired proprioception. In addition, she exhibited proximal upper and lower limb weakness, neck flexion weakness, and areflexia.

Cerebrospinal fluid analysis, performed 6 days after symptom onset, disclosed albuminocytologic dissociation (protein 1.25 g/L [reference range: 0.15-0.45], absent white cells). Cytology was negative for malignant cells and

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Table 1. NCS Performed 12 Days After Symptom Onset.^a

	CV (m/s)	Amp (mV)	DML (milliseconds)	F (milliseconds)
Motor nerves				
R median	50.0 (>46)	6.2 (>5.0)	7.9 (<4.3)	31.93 (≤ 31)
R ulnar	58.0 (>48)	7.5 (>5.8)	6.5 (<3.5)	32.55 (≤ 32)
R/L Comm peroneal (EDB)	36.7 (>38)	0.7/0.2 (>2.2)	14.5/5.8 (<6.0)	
R/L Comm peroneal (Tib Ant)	53.3/52.1 (>38)	2.1/1.9 mV (>2.2)	4.9/4.9 (<6.0)	
R/L tibial (FHB)	39.4/36.7 (>35)	2.8/2.2 mV (>2.0)	16.3/14.7 (<5.8)	59.27/61.72 (≤ 56)
Sensory nerves				
R median (D2)	43.0 (>45)	2 μV (>5)	3.0 (<3.5)	
R ulnar (D5)	49.2 (>43)	2 μV (>4)	2.0 (<3.3)	
R/L sural	48.0/45.5 (43)	5/5 μV (>3)	1.9/2.0 (<4.4)	
R/L Sup peroneal	48.0/43.6 (> 40)	5/6 μV (>6)	2.1/2.3 (<4.4)	

Abbreviations: Amp, amplitude; Comm Peroneal, Common Peroneal; CV, conduction velocity; DML, distal motor latency, EDB, extensor digitorum brevis; FHB, flexor hallucis brevis; L, left; NCS, nerve conduction studies; R, right; Sup peroneal, superior peroneal; Tib Ant, tibialis anterior.

^aNormal values in brackets.

Table 2. Somatosensory Evoked Potentials.

Nerve	Plat 9 N (milliseconds)	Plat N13 (milliseconds)	Plat N20 (milliseconds)	Plat 9 N (milliseconds)	Plat N20 (milliseconds)	Plat P37 (milliseconds)
R/L median	13.5/0 (9.6 ± 0.7)	19.0/19.3 (<13.2 ± 0.8)	24.9/24.2 (<18.9 ± 1.0)			
R/L tibial				13.3/14.2 (6.13 ± 0.76)	ABSENT (16.48 ± 1.262)	52.0/54.0 (38.3 ± 3.3)

oligoclonal bands were negative. Nerve conduction studies, performed 12 days after symptom onset, demonstrated a demyelinating sensorimotor polyneuropathy with prolonged F wave responses in the upper and lower limbs along with absent H reflexes (see Table 1). Blink reflexes were normal. The median and tibial nerve somatosensory sensory evoked potentials were prolonged (Table 2). Autoimmune screen was negative, apart from a mildly elevated rheumatoid factor (titer 21 IU/mL, <15) and mildly positive ANA (titer of 1:160, speckled pattern). The remaining investigations, including antiganglioside GQ1b antibodies, infective, and metabolic screen, were all negative. Magnetic resonance imaging of brain and spine was normal.

She was treated initially with combined intravenous immunoglobulin 2 g/kg in 5 divided daily doses and intravenous methylprednisolone 1000 mg daily for 5 days, followed by a weaning dose of oral prednisolone. She made modest clinical improvement and was later transferred to a rehabilitation unit for further gait and balance exercises. The patient required additional plasmapheresis with significant functional improvement and remains currently on maintenance immunoglobulin infusions and prednisolone. At the most recent review, she had complete recovery in gait, ptosis, and extraocular movements and, however, was noted to remain areflexic. Unfortunately, despite an initial partial response to treatment, she had progressive disease on routine staging scans and was commenced on dabrafenib and trametinib.

Discussion

Miller Fisher syndrome is considered a subtype of Guillain-Barre syndrome (GBS) and is characterized by the clinical triad of ataxia, areflexia, and ophthalmoplegia.⁴ There are several antiganglioside antibodies associated with GBS and its subtypes. Miller Fisher syndrome is usually associated with an antecedent infection, resulting in aberrant production of antibodies directed against GQ1B gangliosides.⁵ Anti-GQ1B antibodies are located in paranodal myelin of cranial nerves innervating extraocular muscles and dorsal root ganglion explaining the cardinal features of MFS. Anti-GQ1b antibodies are also associated with Bickerstaff encephalitis and the pharyngeal–cervical–brachial weakness variant of GBS.⁶

There is a diverse range of neurological immune-mediated adverse events associated with immunotherapy including facial nerve palsies,⁷ chronic immune demyelinating polyneuropathy,⁸ transverse myelitis,⁸ and posterior reversible encephalopathy syndrome,⁹ encephalitis,¹⁰ GBS,¹¹ and myasthenia gravis (MG).¹² To date, there are no case reports documenting MFS as a consequence of immunotherapy for the treatment of melanoma.

In the present case, MFS likely occurred as a consequence of immunotherapy for the treatment of melanoma, given the temporal association between commencement of therapy and development of symptoms. There is conflicting evidence regarding the presence of the associated autoantibody in

neurologic immune-mediated adverse events. Suzuki et al¹² recently examined the characteristics of nivolumab-associated MG and found seropositivity at a similar frequency to a control group of patients with idiopathic MG. Others, however, have reported seronegativity similar to our patient.¹³

Immunotherapy toxicities vary in their severity but there are case reports of fatalities.¹⁴ One important therapeutic consideration is that although these toxicities are a consequence of T-cell activation, there may be additional “downstream” components of the inflammatory response that respond to traditional therapies such as immunoglobulin or plasmapheresis. Management should focus on discontinuation of the immunomodulatory in addition to immunosuppression with high-dose corticosteroid in suspected cases^{3,15} and consideration of adjunctive immunoglobulin/plasmapheresis. In the present case, both immunoglobulin, high-dose corticosteroid and plasmapheresis were used, reflecting both this uncertainty and severity of the presentation. It is important to recognize immune-related adverse events early so that timely and adequate treatment is provided.

Authors' Note

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The patient reported here provided informed consent for the publication of this article.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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