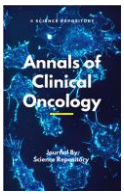

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Case Report and Review of Literature

Management of myasthenia gravis without significant exacerbation during nivolumab therapy for metastatic melanoma: a case report and review of literature

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ABSTRACT

A 51-year-old man with myasthenia gravis (MG) and metastatic melanoma had progression of his melanoma with supratentorial metastases on dabrafenib-trametinib and was transitioned to anti-PD1 immunotherapy with nivolumab. He presented to the hospital soon after starting nivolumab with headache, mild diplopia, and right-sided dysdiadochokinesia and reduced proprioception. EMG showed a mildly increased percentage of fiber pairs with increased jitter without impulse blocking, and MG outcome measures were worse, consistent with mild exacerbation. He continued to receive pyridostigmine, and after discharge showed functional improvement and return of his MG outcome measures to baseline. Nivolumab was continued for three months without further MG exacerbations until disease progression in the liver, mesentery, and lung. Close monitoring of neurological autoimmune conditions by neurology in conjunction with oncology could help ensure greater patient safety during anti-PD1 immunotherapy treatment in MG patients. We recommend pursuit of larger trials to clarify immunotherapy safety profiles in such patients.

Background

The past decade has seen a revolution in the treatment of metastatic melanoma (MM). Since the FDA approval of the anti-CTLA-4 monoclonal antibody ipilimumab in 2011, single-agent and combination immunotherapies have become an integral component of the management of unresectable or metastatic melanoma. The anti-PD-1 agents nivolumab and pembrolizumab, developed soon after, demonstrated improved objective response rates and progression-free survival, in addition to lower incidence of treatment-related adverse events of grade 3 or higher in comparison to ipilimumab. These, along with combination nivolumab/ipilimumab therapy, have become first-line therapies for MM regardless of BRAF mutation status [1, 2]. As a treatment modality that promotes immune response enhancement, immunotherapy is associated with an adverse event profile including immune-related adverse events (irAEs) affecting a spectrum of organs and organ systems, notably the nervous system. Anti-CLTA-4 and anti-PD-1 therapies have even been reported to induce conditions such as acute inflammatory demyelinating polyneuropathy (AIDP), myositis, and myasthenia gravis (MG) [3-12]. Understandably, there is reluctance among physicians to prescribe immune checkpoint inhibitors to patients with preexisting autoimmune conditions such as MG out of concern for enhanced autoimmune reactivity triggering irAEs of increased frequency

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or severity, or even acute autoimmune crisis. In fact, the NCCN 2019 guidelines state that "Patients with underlying autoimmune disorders are generally excluded from treatment with checkpoint immunotherapies [13]".

Here, we report a patient with MM and concomitant MG who was treated with the anti-PD-1 therapy nivolumab. The treatment was well-tolerated with no evidence of severe MG exacerbation observed during the course of treatment.

Case Presentation

In July 2008, a 44-year-old man was diagnosed with stage T3b invasive melanoma of his right lower back. No metastatic disease was found on wide excision and a sentinel lymph node biopsy, and the patient was treated with a month of high-dose adjuvant interferon alpha followed by 11 months of maintenance-dose interferon alpha. In late 2010, he developed bilateral lower extremity weakness which progressed to his upper extremities with muscle aches and a cold, burning sensation in his legs, followed by chronic cough and dyspnea, night sweats, stuttering speech, and blurred vision. Radiological studies showed no abnormalities. Single-fiber electromyography (SFEMG) in March 2011 was consistent with a mild defect of neuromuscular transmission, but repeat SFEMG was normal without decrement or facilitation, and a needle examination of his limb muscles was normal. On laboratory evaluation there was no evidence of Lyme's disease or other infection, thyroid dysfunction, Lambert-Eaton syndrome, or myopathy, and no autoantibodies against acetylcholine receptor or striated muscle. However, his weakness improved on pyridostigmine, and a subsequent physical exam demonstrated mild limb weakness, proximal greater than distal, and asymmetrical ptosis. He was diagnosed with seronegative MG.

In February 2015, metastatic melanoma positive for BRAF V600E mutation was diagnosed in his liver and small bowel. He began treatment with dabrafenib and trametinib after jejunal resection. His treatment course was complicated by hepatitis requiring prednisone and one hospitalization. Numerous sub-centimeter brain metastases to both frontal and parietal lobes were discovered on PET/CT and MRI in September 2015, prompting the decision to discontinue dabrafenib-trametinib and begin whole-brain radiation therapy (WBRT). Therapeutic options and goals of treatment were discussed with the patient over several encounters with his oncologist and his neurologist. The patient verbalized understanding of the risks of immunotherapy given his underlying MG, and he accepted these risks. He began treatment with nivolumab in October. He continued to see his neurologist for MG management, which was monitored using four validated MG outcome measures at each office visit: MG-Activities of Daily Living score (MG-ADL), MG-Quality of Life score (MG-QOL15), MG-Manual Muscle Test score (MG-MMT), and MG-Composite score (MGC).

Later that month, the patient was admitted to the hospital with constipation, worsening nausea and vomiting, right arm and hand numbness and paresthesia, and a worsening occipital headache with neck stiffness. Neurological examination was notable for mild diplopia on sustained up-gaze without ptosis or other facial weakness, as well as decreased proprioception and slowed rapid alternating movements in the right hand. Initial treatment on admission consisted of SMOG (saline, mineral oil, and glycerin) enemas and a bowel regimen, prochlorperazine and acetaminophen.

Investigations

The differential diagnosis for the patient on admission included myasthenia gravis exacerbation and/or intracranial events cause by electrolyte imbalances, worsening brain metastases, intratumoral hemorrhage, or increasing metastatic disease burden. Serum electrolytes and chemistries measured on admission were normal other than a mildly elevated phosphate (4.9 mmol/L; normal:2.4-4.5 mmol/L) and though a serum LDH was not measured on admission, LDH from earlier that month had been elevated to 1728 U/L. Negative inspiratory force within normal limits. The patient was found to have normal oropharyngeal swallow function. EEG found mild diffuse slowing indicative of bihemispheric dysfunction. SFEMG at this time found increased mean consecutive difference (MCD) which was similar to one month before, but with a mildly increased shift in the percentage of fiber pairs with increased jitter without impulse blocking from the prior study. The patient's MG outcome scores were minimally worse from baseline consistent with a mild myasthenic exacerbation.

Treatment

On admission he was initially given dexamethasone and discontinued on day 2. The patient continued to receive his pyridostigmine while hospitalized. Gabapentin was added to his medication regimen for his right-hand numbness.

Outcome and follow-up

The patient was discharged after a three-day hospital stay; diagnosed with a mild MG exacerbation. The patient's neurological findings apart from diplopia, however, were attributed the patient's brain metastases. Follow-up five days after discharge, the patient was stronger with returning right hand function. His myasthenia gravis scores returned to baseline. LDH at this time had reassuringly continued to trend downwards from prior to admission from 1728 to 1115 U/L. Brain MRI in December that year demonstrated interval increase from September in the conspicuity and number of bilateral supratentorial brain lesions, as well as increased intrinsic precontrast T1 signal in a left parietal metastasis consistent with intratumoral hemorrhage, with restricted diffusion consistent with infarct. The patient continued to receive nivolumab after discharge. Given the increase in brain metastases, Cyberknife treatment was given to his three parietal and three frontal lesions on days 81 and 83 of nivolumab treatment, respectively. His myasthenia gravis scores remained unchanged, indicating a stable MG course throughout most of the treatment period without indication of MG progression (Table 1). Three months into nivolumab treatment disease progressed in the liver, mesentery and lung. He was subsequently switched to vemurafenib and cobimetinib. He remained on this combination for over a year until February 2017, when he was transitioned to palliative care. He subsequently had no further exacerbations of his MG and deceased from complications of his metastatic disease.

Table 1: MG-ADL, MG-QOL15, MG-MMT, and MGC scores. MG-ADL -- Myasthenia Gravis Activities of Daily Living (0-24); MG-QOL15 -- Myasthenia Gravis Quality of Life (0-60); MG-MMT - Myasthenia Gravis Manual Muscle Test (0-120); MGC -- Myasthenia Gravis Composite (0-50). Lower scores correlate with fewer symptoms (MG-ADL), increased quality of life (MG-QOL), reduced disease severity (MG-MMT), and better clinical status (MGC).

Date of Visit	MG-ADL	MG-QOL15	MG-MMT	MGC
09/15/2015	3	4	2	5
10/08/2016 -- Nivolumab therapy initiated				
10/08/2015	2	10	3	3
10/14/2015	7	44	11	15
10/20/2015	4	40	2	4
11/03/2015	5	15	3	3
11/17/2015	2	7	3	1
12/03/2015	0	15	2	1
01/14/2016	1	13	2	1
01/21/2016 -- Nivolumab therapy discontinued				

Discussion

MG is a B-cell and complement mediated autoimmune disorder targeting the neuromuscular junction. Its cardinal feature is fatigable weakness typically affecting the ocular muscles – causing commonly-recognized symptoms of ptosis and diplopia – as well as proximal limb, bulbar, and respiratory muscle group weakness. This is most commonly due to an autoantibody against acetylcholine receptor (AChR) with induction of the complement membrane attack complex. Much less frequently patients will have antibody to muscle-specific tyrosine kinase (MuSK) protein or antigen targets of lipodensity receptor protein (LRP) 4 and agrin. The detection of these antibodies in patients is highly specific for diagnosis of MG [14, 15]. However, there is a subset of patients who, despite having the clinical features of MG, lack detectible autoantibodies. These patients are diagnosed by the clinical history, response to cholinesterase inhibitors and electrophysiological examination of synaptic transmission with the exclusion of alternative diagnoses. They are classified as seronegative MG patients. MG is often monitored through outcome measures such as an MG-Activities of Daily Living score (MG-ADL), an MG-Manual Muscle Test score (MG-MMT), an MG-Composite score (MGC), and an MG-Quality of Life score (MG-QOL), which help track symptom severity, disease severity, clinical status, and quality of life, respectively [16-19]. There is some evidence linking CTLA-4 to MG, with MG patients demonstrating reduced expression of CTLA-4 on T-cell membranes, as well as certain single nucleotide polymorphisms in the *CTLA-4* promoter region affecting its expression in MG [20-22]. On the other hand, little biochemical evidence exists to show a connection between PD-1 and MG [23]. However, case reports have detailed the manifestation of MG in patients treated with ipilimumab-nivolumab combination therapy [3] as well as nivolumab or pembrolizumab alone, sometimes with fatal results [6-12]. Aggravation of autoimmune disease in the context of anti-PD-1 therapy has also been documented, in particular with MG and pembrolizumab, and in one instance a severe and highly refractory flare of MG in the context of nivolumab [24-28]. Guidelines exist for management of severe MG induced by immune checkpoint inhibitors including the use of methylprednisolone, and plasmapheresis or IVIG if there is no improvement [29]. Interestingly, there are also reports of MG being induced by interferon alpha for patients with chronic hepatitis C; there is a possibility that our patient's MG was actually induced by his adjuvant interferon therapy [30].

Many cases of successful immunotherapy treatment in the context of preexisting autoimmune disease have also been published. Ipilimumab was administered to a patient with multiple sclerosis and another patient with rheumatoid arthritis in one report, with neither suffering from irAEs or autoimmune exacerbation during the course of treatment; the latter benefitted with respect to her melanoma [31]. Another patient receiving ipilimumab with preexisting ulcerative colitis (UC) experienced remission of his UC symptoms rather than exacerbation during treatment, in addition to deriving clinical benefit from ipilimumab [32]. In the realm of anti-PD-1 therapies as well, pembrolizumab was administered to a patient with Churg-Strauss vasculitis without autoimmune exacerbations and successfully reduced tumor burden [33]. Two subjects with MG also received nivolumab and, despite each experiencing an episode of symptom exacerbation consistent with an MG flare, too benefitted from treatment with regression of metastases and stable malignant disease burden, respectively, and resolution of MG symptoms [34, 35]. Our patient too was found to have mild MG exacerbation during nivolumab treatment; however, in the context of his major presenting neurological symptoms, due to progression of his brain metastases or, less likely, a nivolumab-induced flare of his brain metastases, his MG findings were merely incidental in nature and minimally contributed to his overall clinical status. He went on to successfully receive the following six doses of nivolumab, up until disease progression, with no indications of MG flare.

A retrospective study was published in February 2016 investigating irAE frequency and episodes of autoimmune flares in thirty metastatic melanoma patients with preexisting autoimmune conditions, including two with multiple sclerosis and one with transverse myelitis, who received ipilimumab therapy. The report found that irAE incidence among these patients was in fact no higher than the observed incidence in ipilimumab clinical trials, and for the majority of patients who did experience either an irAE or an autoimmune disease exacerbation, their events were well-managed with standard therapies, and ultimately they benefitted from having received ipilimumab [36]. Our paper differs from other reports because of the joint work between oncology and neurology to manage the patient's MG for the duration of nivolumab therapy both in the inpatient and outpatient settings, and the use of EMG and MG outcome measures to monitor the patient's MG status. Based on the single case we present, we cannot extrapolate that anti-PD-1 therapy can be used safely in patients with MG or other autoimmune conditions, and their application in such circumstances should continue to be treated with caution. However, it does suggest that preexisting MG need not necessarily preclude clinical benefit from anti-PD-1 therapy, especially when one considers the grim prognosis of MM. In these cases, a partnership between the medical oncologist and the neurologist is critical for close monitoring of MG through careful neuromuscular examination and outcome scores to detect signs of decline prior to onset of crisis. We urge that larger trials be conducted for the use of anti-PD1 therapy in such patients to better ascertain if they might safely be adopted into standard clinical practice.

Learning points

- Clinicians should maintain a low threshold of suspicion for autoimmune worsening in the care of MG patients on cancer immunotherapy who present with new-onset neurological symptoms.
- Close management and monitoring by the patient's neurologist in conjunction with their oncologist can help ensure greater patient safety during the course of treatment for earlier detection of autoimmune exacerbations for oncology patients with preexisting neurological autoimmune disease starting immunotherapy.
- We recommend larger multi-center clinical trials or registries assessing the use of anti-PD1 therapies in patients with preexisting autoimmune disorders, and neurological autoimmune conditions in particular, to further clarify the magnitude of short-term and long-term risks of therapy and associated morbidity and mortality.

Abbreviations

MG – myasthenia gravis; MM – metastatic melanoma; irAEs – immune-related adverse events; SFEMG – single-fiber electromyography

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