

Myasthenia Gravis Exacerbation Following BRAF and MEK Inhibitor Therapy

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Introduction

While there is a well-known association of immune check point inhibitors and myasthenia gravis (MG), there has also been three previous cases of new onset MG being associated with B-Raf proto-oncogene serine/threonine-protein kinase (BRAF) and/or mitogen-activated protein kinase (MEK) inhibition treatment. The previously associated medications include binimetinib (MEK inhibitor) and the combination of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor).¹⁻³ We report a novel case of a patient with well controlled generalized MG who developed exacerbation after treatment for metastatic melanoma with vemurafenib, a BRAF inhibitor, and cobimetinib, a MEK inhibitor.

Case Presentation

An 84-year-old male with a history of MG, chronic obstructive pulmonary disease, hypertension, and melanoma on the right chest, status post resection 4 years prior, presented with left posterior rib cage pain. CT of chest and abdomen revealed innumerable bilateral pleural nodules and scattered hypodensities in the liver, and MRI found a small enhancing cerebellar lesion, all concerning for metastasis. An excisional biopsy of an enlarged right supraclavicular lymph node was consistent with metastatic melanoma with BRAF mutation. A plan to treat with nivolumab and ipilimumab was discussed. Due to his prior MG history, a neuromuscular consultation was requested to evaluate the pros and cons of the above immune-check point inhibitor therapy.

The patient presented 6 years prior with symptoms of diplopia, ptosis, and dysphagia. Acetylcholine receptor binding and modulating antibodies were elevated at 11.5 nM and 80%, respectively. Striational antibodies were positive at a titer of 1:7680. CT chest revealed a thymoma which was subsequently removed via robotic right thoracoscopic thymectomy. Pathology revealed a non-invasive thymoma of the AB type, modified Masaoka stage I. His myasthenia was initially treated with prednisone and maintenance plasma exchange for about 2 years. Mycophenolate mofetil therapy was initiated later and plasmapheresis was discontinued. At the time of metastatic melanoma

diagnosis, the patient had a normal neurologic examination. His immunosuppression regimen included prednisone at 5 mg daily and mycophenolate mofetil 500 mg twice daily. It was thought that his MG control was optimized to allow treatment with nivolumab and ipilimumab.

Patient was given a single infusion of nivolumab which did not alter tumor growth. No further nivolumab nor ipilimumab were given. Three months later, treatment was transitioned to vemurafenib and cobimetinib. After being on this combination therapy for 2 weeks, the patient presented with significant worsening of his myasthenic symptoms that included ptosis, diplopia, dysphagia, and dyspnea. He was intubated for myasthenic crisis. High dose corticosteroid therapy of prednisone 60 mg daily and plasmapheresis were initiated, without leading to clinical improvement. Due to the poor prognosis of his metastatic melanoma, the patient and family elected for conservative treatment without further escalation of care. The patient died 16 days after presentation with MG exacerbation.

Discussion

Immune check point inhibitors inducing or exacerbating myasthenia gravis (MG) have been well reported in the literature.⁴⁻⁶ To our knowledge, this is the first reported case of vemurafenib and cobimetinib causing MG exacerbation. A literature review reveals that such a combined treatment could result in subacute immune-mediated motor polyneuropathy.⁷ In addition, three cases of MG development or exacerbation following similar BRAF and/or MEK inhibitor therapy have been reported previously.¹⁻³

The mechanism by which BRAF and MEK inhibition could cause development or exacerbation of MG is currently still unknown. Demichelis et al. proposed possible mechanisms of off-target effects on tyrosine kinases that could alter the structure, stability, or function of the neuromuscular junction and/or decreased immune surveillance that may enhance autoimmunity.⁷

As these novel immune therapies are increasingly used in metastatic melanoma, clinicians should be aware of their associated risk of exacerbating MG and causing other immune-mediated neuromuscular disorders.

Disclosures

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Conflict of Interest: None

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