

CLINICAL VIGNETTE

Immunotherapy Induced Myasthenia Gravis

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Case Presentation

A 70-year-old female was initially diagnosed with invasive lobular carcinoma twenty years prior. Her tumor was ER/PR positive, HER2 non-amplified and she underwent mastectomy and axillary lymph node dissection with 18 out of 19 lymph nodes positive. She had otherwise negative staging evaluation and underwent adjuvant chemotherapy with TAC, adjuvant radiation therapy followed by 10 years of anastrozole. Seven years ago she developed back pain with imaging showing intra-abdominal and pelvic lymphadenopathy, uterine metastasis as well as osseous disease. Biopsy confirmed recurrent disease. She was treated with three prior lines of therapy and was found on NGS testing to have high tumor mutational burden (TMB) with 20 Muts/Mb. Based on Keynote 158 trial which was tumor agnostic approval of pembrolizumab based on TMB >10 Muts/Mb,¹ we elected to treat, and she received 2 doses. Following the second dose she complained of fatigue and was evaluated for endocrinopathy with initially negative testing, but progressive symptoms with difficulty opening eyes, weakness and difficulty swallowing prompted admission.

On arrival the patient was afebrile and hemodynamically stable. She had oxygen saturation of 94% on room air but with subjective difficulty taking a deep breath. Physical examination demonstrated left eye ptosis, worsened with sustained upward gaze, which improved with application of ice pack for 2 minutes.² Extraocular muscles were intact, and the patient denied any diplopia. The remainder of the neurological examination was unremarkable. TSH and cortisol levels were normal. CT of the chest did not show any findings of SVC syndrome, pneumonitis or thymoma. MRI of the brain did not reveal any abnormalities including within the pituitary gland. Troponin level was elevated at 108 ng/L (0 - 54 ng/L) with a stable trend and no associated acute EKG changes. Echocardiogram did not demonstrate any dysfunction or wall motion abnormalities. Acetylcholine receptor blocking antibody later returned positive at 0.38 nmol/L (0 - 0.24 nmol/L). The patient was treated in the hospital with IV methylprednisolone 100 mg daily and pyridostigmine 60 mg three times daily with mild improvement in dysphagia and dyspnea, with normalization of oxygen saturation. She was discharged on high dose prednisone 80 mg daily, and continued on pyridostigmine, leading to partial response in symptoms, and had improvement allowing for weaning of steroids with initiation of ongoing IVIG. At time of submission, she improved, without complete resolution of myasthenia symptoms.

Discussion

Myasthenia gravis (MG) is an autoimmune disorder affecting the postsynaptic neuromuscular junction caused by autoantibodies to the acetylcholine receptors. Symptoms typically include ptosis and diplopia, but can progress to limb weakness, dyspnea and respiratory failure. Pembrolizumab, a monoclonal antibody which targets PD1, is among the class of treatments labeled immune checkpoint inhibitors (ICIs), with widespread use in multiple malignancies, with several similar agents FDA approved. Although sometimes severe, immune related toxicities including pneumonitis, colitis, hepatitis and endocrinopathies are well described, and theoretically have the potential to cause any autoimmune spectrum of illnesses. We present a rare patient that was recently initiated on immunotherapy who developed symptoms of myasthenia gravis. Although secondary myasthenia gravis was not well described in early trials of ICI, clear case reports have been published and one of the largest literature and institutional reviews report <0.25% incidence.³ The pathophysiology is unknown, however in case studies, symptoms typically develop within weeks of initiation treatment with ICI. Severity of symptoms has been reported to be worse in patients receiving combination therapy as opposed to monotherapy. The treatment for immunotherapy induced myasthenia is the same as for MG: cholinesterase inhibitors for mild disease; high dose steroids (with monitoring for transient worsening of symptoms); IVIG and PLEX for moderate to severe disease.⁴ Immunotherapy has been discontinued for our patient, given severity of reaction, and incomplete resolution of symptoms and there is no imminent plan for rechallenge therapy. In situations as rare as this, there were limited data for optimal initial therapy, let alone risks of retreatment. Troponin elevations have been associated with myasthenia, and may also represent a myocarditis phenomenon from immunotherapy itself. Thankfully our patient did not show evidence of severe cardiac disease on echocardiography.

This case is an example of a rare but serious and life-threatening complication to her therapy, with very clear clinical symptoms to aid in diagnosis of future cases, and to elucidate the limited available data to direct management.

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