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Pembrolizumab-induced myasthenia gravis: Two patients' experiences

Leslie Montag [a,*], Rachael Piver [b], Amy Vidalin [c], Marian Johnson [b], Bunja Rungruang [b], Robert Higgins [b]

[a] Medical College of Georgia, Augusta, GA, United States
[b] Division of Gynecologic Oncology, Medical College of Georgia at Augusta University, Augusta, GA, United States
[c] Department of Obstetrics and Gynecology, Medical College of Georgia at Augusta University, Augusta, GA, United States

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ABSTRACT

Checkpoint inhibitors are increasingly used to treat patients with gynecologic malignancies and can cause rare and unusual side effects, also known as immunotoxicities, that are rarely observed in patients receiving traditional immunotherapy. If these are not identified and treated, they can cause disability and even death for patients undergoing treatment. This report describes the range of pembrolizumab-induced myasthenia gravis (MG) immunotoxicity through two cases. The first patient is an 85-year-old woman with recurrent vulvar carcinoma who completed two cycles of pembrolizumab. She had a severe presentation leading to respiratory failure. The second patient is an 80-year-old woman with recurrent serous endometrial carcinoma who developed isolated ocular myasthenia after her second cycle of pembrolizumab. The symptoms and physical examination findings described here illustrate the breadth of symptom severity associated with pembrolizumab-induced MG and importance of early identification and treatment to minimize symptoms and improve outcomes.

1. Introduction

Immune checkpoint inhibitors (ICI) are a novel class of immunotherapy, each targets a known molecular marker that allows cancer cells to evade the immune system. The inhibition of these receptors, or checkpoints, allows for the immune system to mount an anti-tumor response. PD-1 and PD-L1 inhibitors block the interaction between PD-1 and PD-L1, allowing T cells to recognize and neutralize tumor cells (Flynn and Gerriets, 2023; Goleva et al., 2021). Pembrolizumab, an anti-PD-1 monoclonal antibody, was initially approved by the Food and Drug Administration (FDA) in September 2014 for treatment of advanced refractory melanoma (Flynn and Gerriets, 2023). Over the last decade, its indications have widely expanded to include most solid tumor malignancies with high microsatellite instability (MSI-H) or mismatch repair defect (dMMR) (Flynn and Gerriets, 2023).

As pembrolizumab is a monoclonal antibody, it has the potential for cross-reactivity with healthy tissue. The reaction to healthy tissues is known as immunotoxicity, or immune-related adverse events (irAEs). This reaction can occur in any organ system and up to 90% of patients experience some level of immunotherapy toxicity (Goleva et al., 2021). Neurological irAEs are observed in approximately 14% of patients on ICI therapy (Bolz et al., 2021). One rare, but serious neurotoxic effect is immune-related myasthenia gravis (irMG). Here we present two cases of pembrolizumab-induced myasthenia gravis that show the breath of presentation and severity of this unusual toxicity. A summary of both patient cases can be seen in Table 1.

2. Patient Case 1

An 85-year-old female with recurrent vulvar squamous cell cancer was initially diagnosed in 2013 with stage IB vulvar cancer and underwent radical vulvectomy with bilateral inguinal lymph node dissection. She required 2 additional simple partial resections of dysplasia, and in November 2020, she had a vulvar biopsy of a 2 cm lesion, pathologic diagnosis consistent with recurrent vulvar cancer with lymphvascular invasion. She declined surgery and was treated with external beam radiation therapy to the vulva and groin. In January 2023, she developed a necrotic inguinal lymph node, biopsy consistent with recurrent vulvar cancer. Patient was offered chemotherapy but declined treatment. Tumor molecular profile indicated PD-L1 positivity, and she agreed to treatment with pembrolizumab, completing two cycles.

Eleven days after her second treatment of pembrolizumab, she presented to clinic with one week of worsening neck and back pain, thought to be musculoskeletal. Two days later, she presented to the emergency

* Corresponding author at: Medical College of Georgia at Augusta University 1120 15th Street Augusta, GA 30912, USA.
E-mail address: lmontag@augusta.edu (L. Montag).

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Table 1
Summary of Patient Case 1 and Patient Case 2.

	Patient Case 1	Patient Case 2
Demographics	85 years old Female Caucasian	80 years old Female Caucasian
Diagnosis requiring Pembrolizumab treatment	Recurrent vulvar carcinoma with PD-L1 positive inguinal lymph node	Recurrent endometrial serous adenocarcinoma
Notable medical history	Type 2 diabetes mellitus Hypertension Hyperlipidemia HFrEF (LVEF 20–25 %) CAD Recent LLE DVT (on Apixaban) Osteoporosis Urinary incontinence Glaucoma	Hypertension Hyperlipidemia Atherosclerosis of carotid arteries Obstructive sleep apnea Anemia Obesity Hx of transient ischemic attack Hx of left breast cancer FHx of myasthenia gravis in father
Onset of symptoms	11 days after cycle 2 Pembrolizumab alone	14 days after cycle 2 of Pembrolizumab plus Lenvatinib
Symptoms	Bilateral ptosis Worsening vision Headache Neck weakness/stiffness Dysphagia Worsening of urinary incontinence Respiratory distress (worsening, developed later in clinical course)	Unilateral ptosis Diplopia Worsening vision
Clinical classification (based on MGFA grade (Myasthenia Gravis Foundation of America, 2023))	Grade III-IV	Grade I
Notable Workup	WBC 12.9 thous/mm^3 CK 426 U/L (related to MG) AST/ALT 102/171 U/L (related to immunotherapy) Lactic acid 3.4 mmol/L Anti-AchR Ab, Anti-MuSK Ab, and LRP4 Ab negative MRI brain negative for acute intracranial process or metastatic disease EMG of left orbicularis oculi consistent with myasthenia gravis	CK and aldolase within normal limits Anti-AchR Ab and Anti-MuSK Ab negative CT head negative for acute intracranial process
Treatment given	Pyridostigmine (dose increased up to 90 mg TID before tapering down) Prednisone 30 mg daily (per neurology recommendations) IVIG 2gm/kg total divided over 4 days Methotrexate 15 mg every 7 days (with folic acid daily other than the days of methotrexate administration) PLEX	Pyridostigmine Prednisone
Outcome	Worsening of symptoms, patient elected for hospice care and passed away	Resolution of symptoms with Pyridostigmine with plan for taper to discontinuation Pembrolizumab discontinued Started on Carboplatin and Paclitaxel for further treatment

[a]Clinical Classification determined by Myasthenia Gravis Foundation of America Clinical Classification. Grade I-II is considered mild, grade III is moderate, grade IV is severe, and grade IV represents intubation with or without mechanical ventilation.

Abbreviations: WBC: white blood cell count; CK: creatine kinase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Ab: antibody; PMNs: polymorphonuclear neutrophils; MRI: magnetic resonance imaging; EMG: electromyography; CT: computed tomography; IVIG: intravenous immunoglobulins; PLEX: plasmapheresis.

department (ED) with worsening neck stiffness/weakness, an inability to raise her head, dysphagia, and headaches. She was given Diazepam, with some subjective improvement in her symptoms and discharged home. Three days later, or 16 days after her C2 infusion, she returned to the ED for evaluation of headaches, shortness of breath without chest pain, and persistent neck weakness/stiffness. Her cardiac evaluation showed a normal electrocardiogram, mild troponin elevation attributed to mild heart failure, and no evidence for an acute coronary event, and she was discharged home from the ED. An outpatient optometrist exam completed after her second ED visit noted a significant decline in her vision.

She presented to clinic for follow up 18 days from her C2 infusion with worsening of her symptoms. She was admitted to the hospital. Her exam on admission was positive for profound neck weakness, 4/5 bilateral deltoid weakness, and bilateral ptosis. Her pertinent laboratory values are in Table 1. CK, AST, ALT were all markedly elevated. MG antibody testing was negative, but electromyography of her left orbicularis oculi was consistent with myasthenia gravis (MG). She was treated with intravenous immunoglobulins, pyridostigmine, and daily prednisone for myasthenia gravis induced by pembrolizumab based on the electromyograph. She developed acute respiratory distress, concerning for a myasthenic crisis. She was then treated with methotrexate and underwent regular plasmapheresis, which improved her respiratory status significantly. Unfortunately, she developed severe spasmic abdominal cramping related to pyridostigmine, which did not abate despite diet changes and antispasmodic agents, and the patient declined all additional interventions, desiring to proceed with hospice care. She died seven days later.

3. Patient Case 2

The second patient is an 80-year-old woman with recurrent serous uterine cancer. She was originally diagnosed in December 2020 with stage IIIC2 serous uterine carcinoma. She underwent surgery with TAH/BSO/LND/omentectomy and was treated with standard of care carboplatin and paclitaxel followed by whole pelvis radiation and vaginal brachytherapy with an additional 2 cycles of cisplatin. She developed recurrent disease in January 2023 and started pembrolizumab and lenvatinib. Fourteen days after her second infusion of pembrolizumab, she developed a right eye lid droop. She subsequently developed diplopia and blurred vision 21 days after the infusion. She was managed on an outpatient basis and initially started on dexamethasone with moderate improvement. Her head CT scan, brain MRI, and lab values were unremarkable. Her screening MG antibodies were all negative. The patient quickly followed up with Neuro-oncology and was diagnosed with ocular myasthenia gravis. She was then started on pyridostigmine, which was titrated up to 60 mg TID. She experienced complete resolution of her symptoms over the next few weeks while continuing pyridostigmine without side effects. She was maintained on pyridostigmine for 2 months then tapered off without recurrence of symptoms. A follow up PET scan unfortunately showed concern for disease metastasis, so the patient was started on carboplatin and Abraxane.

4. Discussion

Immune checkpoint inhibitors have allowed for a durable clinical

response for many patients with gynecologic malignancies. As the rate of ICI use increases, so does the likelihood of immune reactions. It is important for providers treating patients on immunotherapies to be vigilant in the recognition of new symptoms, as many adverse events associated with ICIs are not associated with patients receiving traditional chemotherapy.

Since the origin of immunotherapy, descriptions of adverse reactions are increasingly important as there is wide variation in presentation, severity, and mortality, making early identification key to early treatment and improved patient outcomes. Shirai and colleagues first documented immune-related myasthenia gravis (irMG) secondary to ICI therapy in 2015, reporting a case of nivolumab-induced myasthenia gravis and rhabdomyolysis in an 81-year-old woman being treated for metastatic melanoma (Shirai et al., 2016). IrMG can occur sporadically and can also cause a flare in patients with preexisting myasthenia gravis. A single center with significant ICI use completed a chart and literature review compiling 65 patients with diagnosed or probable MG after ICI use. This study, along with others, found that median time from ICI treatment to onset of MG symptoms is on average 4–8 weeks (Safa et al., 2019; Duong et al., 2021). IrMG represents approximately 17% of all neurotoxic irAEs related to ICIs. Notably, high-grade irMG has been reported to be more prevalent, up to 63%, than low-grade irMG (Safa et al., 2019). Dugena and associates reviewed 29 cases and reported that 13 patients had full resolution of their symptoms with treatment (Dugena et al., 2022). Of the irMG subtypes, isolated ocular irMG had the highest rates of full symptomatic resolution (Dugena et al., 2022). The overall mortality rate of irMG has been estimated to be 30–34%, predominantly occurring in patients with diffuse symptoms (Bolz et al., 2021; Duong et al., 2021; Dugena et al., 2022).

There are only two other case reports of irMG in patients with gynecologic malignancies. Gonzalez and colleagues reported a patient with pembrolizumab-induced myasthenia gravis characterized by dysphagia, diplopia, dysarthria, and extra-axial muscle weakness in a patient with metastatic uterine carcinosarcoma (Gonzalez et al., 2017). The patient was treated with pyridostigmine and prednisone with significant symptomatic improvement but died from disease complications two months later. Yuen et al. described a patient treated with Avelumab for refractory metastatic ovarian cancer who developed seronegative myasthenia gravis characterized by respiratory failure (Yuen et al., 2019). Her symptoms resolved with steroids and maintenance IVIG. Our unique case patients demonstrate the variety of symptoms and outcomes that can occur with irMG secondary to pembrolizumab in the treatment of gynecologic cancers.

Providers must be diligent with regards to the subtle symptoms of MG in patients receiving immunotherapy. Myasthenia gravis may be difficult to diagnose due to variable clinical presentations, intermittent symptoms, overlapping symptoms with other conditions including multiple sclerosis and paraneoplastic syndromes, and lack of awareness by health care providers. Lack of specificity on initial routine blood tests and imaging studies can also delay diagnosis. These factors likely contributed to the delayed diagnosis of our first case patient, ultimately resulting in progression of the patient's symptoms and delaying treatment. A comprehensive clinical evaluation with a focus on fluctuating muscle weakness and fatigue, awareness of MG-associated immunotherapy treatments, and prompt referral to a neurologist are important for accurate diagnosis and treatment.

If a patient presents with eyelid droop, muscle weakness, or other findings concerning for irMG, diagnostic testing with AChR and anti-muscle specific tyrosine kinase antibodies are highly specific and sensitive for generalized MG and less sensitive for ocular MG, although patients with irMG may have negative antibody studies (Lazaridis and Tzartos, 2020). If AChR antibodies are negative, testing for muscle-specific kinase (MuSK) antibodies can be diagnostic. Diagnosis can also be made with repetitive stimulation EMG studies or single fiber electromyography (SFEMG), which is the most sensitive test to diagnosis MG. Neurology consultation is important to further assist diagnosis. Finally, a MRI brain/spine is recommended to rule out alternative structural disease processes (National Comprehensive Cancer Network, 2023).

MG can also mimic, or be superimposed on, another myositis: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatine phosphokinase (CPK), and aldolase should be obtained. If CPK is elevated, a cardiac evaluation should also be completed with an EKG, troponin levels, and TTE to evaluate for concurrent immune-related myocarditis (National Comprehensive Cancer Network, 2023). Finally, pulmonary function should be evaluated on diagnosis or presumed diagnosis with pulmonary function tests (PFTs) (Gonzalez et al., 2017). Respiratory failure is the most common cause of mortality for patients with MG, and continued evaluation for respiratory support is often necessary in treatment (Chen et al., 2020). As such, evaluating negative inspiratory force and vital capacity is pivotal to catch this possible complication.

Following a diagnosis of irMG secondary to ICIs, ICI therapy should be held (Dugena et al., 2022; Yuen et al., 2019). Treatment options vary depending on the severity of symptoms and treatment response. The severity is based on a standardized grading created by the Myasthenia Gravis Foundation of America (MGFA) and adopted by the NCCN, and the treatment guidelines were developed by the NCCN (National Comprehensive Cancer Network, 2023; Myasthenia Gravis Foundation of America, 2023). The irMG grading and treatment guidelines are summarized in Table 2. Of note, one retrospective chart review suggested better patient outcomes when treated with IVIG or plasmapheresis regardless of steroid administration as first-line treatment versus steroids alone in irMG patients; however, this has not yet been evaluated in a clinical trial (Safa et al., 2019). Standard of care for patients with myasthenia gravis in myasthenic crises includes IVIG and PLEX and

Table 2
Immune-related Myasthenia Gravis Grading and Treatment Guidelines (National Comprehensive Cancer Network, 2023; Myasthenia Gravis Foundation of America, 2023).

MGFA Grade[a]	Symptoms	NCCN Treatment Guidelines
I	Isolated ocular weakness	– Hold ICI therapy – Consider inpatient management – Pyridostigmine PO starting at 30 mg TID (titrate up to 120 mg four times daily as tolerated) – Low dose prednisone 20 mg PO daily. Increase by 5 mg every 3–5 days for target dose of 1 mg/kg/day but not exceeding daily dose of 100 mg. Taper based on symptomatic improvement.
IIa	Mild weakness affecting predominantly limb muscles or axial muscles or both May have concurrent ocular muscular weakness	
IIb	Mild weakness affecting predominantly oropharyngeal or respiratory muscles, although may affect other muscle groups	
IIIa	Moderate weakness affecting predominantly limb muscles or axial muscles	– Permanently discontinue ICI therapy – Inpatient management – IV methylprednisolone 1–2 mg/kg/day (taper based on symptom improvement) – Plasmapheresis or IVIG – Consider adding Rituximab (375 mg/m^2 weekly for 4 treatment or 500 mg/m^2 every 2 weeks for 2 doses) if refractory to plasmapheresis or IVIG – Frequent PFTs – Daily neurological evaluation – Avoid medications that could worsen MG (examples: beta blockers, fluoroquinolones, IV magnesium)
IIIb	Moderate weakness affecting predominantly oropharyngeal or respiratory muscles	
IVa	Severe weakness affecting predominantly limb muscles or axial muscles	
IVb	Severe weakness affecting predominantly oropharyngeal or respiratory muscles	
V	Requiring intubation with or without mechanical ventilation unless required during routine postoperative management	

[a]Grade I-II is considered moderate severity per NCCN guidelines. Grade III-IV is considered severe.
Abbreviations: MGFA: Myasthenia Gravis Foundation of America. NCCN: National Comprehensive Cancer Network. ICI: Immune checkpoint inhibitor.

should be considered for patients with irMG who present in crisis, despite the paucity of cases (Bird and Levine, 2024).

ICI should be permanently discontinued in the setting of grade 3–4 irMG of MGFA. A retrial of ICI therapy in grade G2 or lower irMG may be attempted, as recurrence of MG symptoms is variable. Some retrial attempts have led to recurrence of irMG symptoms, forcing permanent discontinuation of ICI therapy (Tedbirt et al., 2019). There is some evidence in other disease sites that in the setting of a G2 or lower irMG, retrial of ICI therapy without recurrence of symptoms was possible, if the patient experienced full resolution of symptoms and was kept on maintenance therapy prior to resuming ICI therapy (National Comprehensive Cancer Network, 2023). Dugena et al. note that patients may benefit from resumption of ICI therapy, with concurrent steroid treatment and close monitoring, if their irMG was steroid responsive (Dugena et al., 2022). The decision to restart or discontinue ICI therapy should be made through shared decision making between the provider and the patient.

In summary, immune checkpoint inhibitor therapy-related myasthenia gravis is a severe, potentially life-threatening immune-related adverse event. The two cases we present here demonstrate the range of symptoms and severity of disease of irMG in addition to two different outcomes.

As immunotherapy use continues to increase in gynecologic oncology, so do the immune reactions. However, the diagnosis and management of these responses are mainly documented in case and series reports, rather than through clinical trials. Through this case report, we hope to add to these numbers to better establish risk factors, diagnosis, and management of irMG secondary to ICI therapy to provide both providers and patients better insight into risk factors, diagnosis, and optimal management to improve patient outcomes.

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Leslie Montag: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Rachael Piver:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Amy Vidalin:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Marian Johnson:** Writing – review & editing, Resources. **Bunja Rungruang:** Writing – review & editing, Resources, Conceptualization. **Robert Higgins:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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