

Unmasking Weakness: A Case of Pembrolizumab-induced Myasthenia Gravis With Concurrent Myositis

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ABSTRACT

Immune checkpoint inhibitors (ICIs) have revolutionized modern oncology by enhancing endogenous anti-tumor immunity by targeting multiple regulatory pathways. Despite their efficacy in cancer management, ICIs can cause many immune-related adverse events (irAE), including neurologic adverse events (irNAEs) such as myasthenia gravis (MG)-like syndromes or myositis. We describe the case of an 86-year-old patient with renal cell carcinoma newly treated with pembrolizumab who developed generalized weakness, dysphagia, dysphonia, eyelid ptosis, and ophthalmoparesis shortly after receiving his second dose of pembrolizumab. Examination revealed weak palatal elevation, mild symmetric muscle weakness, mild weakness of neck flexion, and a positive ice-pack test. His workup revealed coexistence of ICI-induced MG and myositis. He was started on high dose corticosteroids, intravenous immunoglobulin, and pyridostigmine, resulting in clinical improvement. ICI therapy was permanently discontinued. ICI-induced NAEs carry significant morbidity and mortality, requiring early recognition, multidisciplinary management, and aggressive immunosuppressive therapy to improve clinical outcomes.

KEYWORDS: immune checkpoint inhibitors; myasthenia gravis; myositis; intravenous immunoglobulin

INTRODUCTION

Immune checkpoint inhibitors (ICIs) are novel agents that have transformed the therapeutic landscape of oncology and are now important in the management of multiple malignancies, including urothelial carcinoma, renal cell carcinoma, non-small cell lung cancer, Hodgkin lymphoma, colorectal cancer, and melanoma.¹ Unlike traditional chemotherapy, ICIs enhance antitumor immunity by modulating endogenous immune responses by restoring T-cell-mediated recognition and destruction of malignant cells.²⁻⁴ Despite this, ICIs are associated with multiple different types of immune-related adverse events (irAE), including neurological adverse events (irNAEs), which may occur in approximately 1 to 12% of patients, varying by ICI therapy type.⁵ These neurotoxicities include but are not limited to

myositis, peripheral neuropathies, myasthenic syndromes, encephalitis, and demyelinating diseases.^{6,7} Among these, ICI-induced myasthenia gravis (MG) is notable for its rapid progression and high mortality rate, especially in combination with other overlapping syndromes.⁸

CASE PRESENTATION

An 86-year-old man with clear-cell renal carcinoma was started on pembrolizumab, an ICI. Approximately six weeks after initiation of pembrolizumab, he developed generalized weakness. Two days after receiving his second dose of pembrolizumab, he developed new bilateral, symmetrical upper and lower extremity weakness, dysphagia, dysphonia, eyelid ptosis, and ophthalmoparesis. He also recently started requiring a walker for ambulation.

Bedside evaluation revealed a negative inspiratory force (NIF) of -30 cm H₂O. Neurologic examination demonstrated bilateral eyelid ptosis, right worse than left, with inability to volitionally open his right eye. The ice-pack test was positive, with improvement in eyelid ptosis. He also had significant ophthalmoparesis, with limited abduction of the left eye. He had weak elevation of the palate, mild weakness in all the extremities, and mild weakness of neck flexion. Muscle stretch reflexes were normal. CT angiography of the head and neck and brain MRI with and without contrast showed no significant abnormalities.

Given high suspicion for a severe myasthenic syndrome with impending respiratory failure, he was admitted to the intensive care unit. He was initiated on methylprednisolone (1 mg/kg/day), intravenous immunoglobulin (0.4 g/kg daily for five days), and pyridostigmine (30 mg three times daily). Acetylcholine receptor (AChR) and muscle-specific kinase (MuSK) antibodies were negative. The presentation was most consistent with an ICI-associated myasthenic syndrome secondary to pembrolizumab, representing a severe immune-related adverse event (grade 3/4).

In light of the known association between ICI-associated MG and myositis, creatine kinase was measured and found to be elevated (>4,000 IU/L). However, there was no clinical evidence of myocarditis. The patient remained in the intensive care unit for close respiratory monitoring. Muscle power and respiratory function gradually improved and creatine kinase normalized. The patient was discharged to a rehabilitation facility on a steroid taper. ICI therapy was permanently discontinued.

DISCUSSION

ICIs are antitumor therapies that enhance pre-existing immune responses by targeting essential regulatory pathways involved in immune response. ICIs inhibit numerous immune checkpoint molecules, including programmed death 1 (PD-1), programmed death ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), and lymphocyte-activation gene 3 (LAG-3), which regulate physiologic anti-tumor immunity. Engagement of these receptors with their respective ligands results in suppression of T-cell proliferation, differentiation, and effector function. Tumor cells exploit these existing physiologic immune checkpoints, thereby suppressing cytotoxic T cell activity and evading immune surveillance. ICIs disrupt the interactions between receptors and their respective ligands, thereby restoring tumor cell destruction without a direct cytotoxic effect.^{1,4}

Despite their therapeutic efficacy, ICIs are associated with irAE as a result of excessive dysregulated T-cell proliferation, cytokine release, and autoantibody production, leading to cytotoxic injury across multiple organ systems.^{2,4} The severity of irAEs, including irNAEs, are graded on a five-point scale based on the Common Terminology Criteria for Adverse Events by the National Cancer Institute, ranging from grade 1 (asymptomatic), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening), and grade 5 (death). Although grade 3–5 neurotoxicities occur in less than 1% of irAEs,⁹ their potential severity warrants immediate recognition and intervention.

The incidence of irNAEs varies by ICI therapy type, ranging from 1–12%. The incidence is approximately 3.8% with anti-CTLA-4 therapy, 6.1% with anti-PD-1 therapy, and 12% with combined anti-CTLA-4 and anti-PD-1 therapy.⁵ However, real-world retrospective data from a single-institution study of 1,834 patients suggests a slightly higher incidence of approximately 1.5%.¹⁰ The severity of irNAEs may be greater with combination immunotherapy than with monotherapy.

Among irNAEs, neuromuscular events predominate, occurring three times more frequently compared to those

involving the central nervous system. One systematic review involving 428 patients with nAEs found that myositis with or without MG overlap was the single most commonly reported nAE. The relative frequencies of other irNAEs are noted in **Table 1**.^{5–7}

ICI-induced MG may occur as part of an overlapping syndrome known as “triple M syndrome,” which is characterized by myositis and myocarditis coexisting with MG. Distinguishing isolated ICI-induced MG from “triple M syndrome” is critical as the latter carries a higher mortality rate, approaching 62.5%, compared with approximately 29.8% for PD-1 inhibitor-associated MG.¹¹ Furthermore, 40–64% of patients with “triple M syndrome” require mechanical ventilation and intensive care unit level of care.^{12,13}

Approximately 37% of patients with ICI-induced MG can present with concurrent myositis.¹³ The presence of myositis significantly increases the risk of clinical decompensation. Respiratory failure occurs in approximately 54% of patients with concurrent myositis compared with 42% in those with isolated MG.¹⁴

Early and aggressive treatment of severe irNAEs has been associated with improved survival and prevention of progression of further neurologic disability.⁶ Case series have shown that patients with “triple M” or overlapping syndromes such as concurrent MG and myositis who received early intervention with intravenous immunoglobulin (IVIG) and high-dose steroids have more favorable outcomes.^{13–15} The recommended treatment for severe presentations, including overlapping syndromes, includes high-dose steroids in combination with IVIG or plasmapheresis, with escalation to immunosuppressive agents such as rituximab or mycophenolate mofetil when clinically indicated.^{14,15} Despite this, in one study of 65 patients with ICI-induced MG, only 19% of patients achieved full resolution of symptoms while 55% had partial improvement.¹⁴

Distinguishing ICI-induced MG from classic autoimmune MG is critical as the prognosis varies substantially. Clinically, ICI-induced MG resembles classic autoimmune MG, with patients presenting with ptosis, diplopia, fluctuating

Table 1. Relative frequency and distinguishing features of different immune-related neurological adverse effects (irNAEs)

Type of irNAEs	Relative frequency among irNAEs (%)	Key features
Myositis (with or without myasthenia gravis overlap)	32	Proximal muscle weakness, myalgias, elevated creatinine kinase. May have ocular and bulbar symptoms even in absence of myasthenia gravis
Guillain-Barré syndrome and other peripheral neuropathies	22	Sensory or motor deficits, hyporeflexia or areflexia, autonomic dysfunction
Myasthenic syndromes	14	Ocular and bulbar symptoms, neck flexion weakness, respiratory failure
Encephalitis	13	Altered mental status, seizures, inflammatory findings on cerebrospinal fluid
Cranial neuropathies	7	Unilateral or bilateral involvement of cranial nerves
Aseptic meningitis	3	Altered mental status, meningismus
Transverse myelitis	2	Contrast enhancement on spine MRI, inflammatory cerebrospinal fluid findings

muscle weakness, bulbar involvement, and in severe cases, respiratory depression.⁸ While classic MG carries a mortality rate of approximately 6%, ICI-induced MG is associated with a higher mortality, emphasizing the need for a heightened clinical suspicion.⁸

The diagnosis of ICI-induced MG remains primarily clinical and should ideally involve early neurologic evaluation to facilitate timely, life-saving interventions.^{15,16} Early neurologic evaluation not only supports accurate identification of irNAEs and consideration of other neurologic diagnoses, but also helps guide appropriate immunosuppressant dosing.¹⁶ Notably, studies indicate that, in the outpatient setting, only three out of ten patients initially suspected of having irNAEs retain their original diagnoses following a comprehensive neurologic evaluation, suggesting that earlier inpatient neurological assessment may reduce diagnostic revisions.¹⁶ Early neurologic evaluation also aids in risk stratification, helping determine the need for escalation of care at a given point in the patient's course given the risk of respiratory decompensation.^{15,16}

Neurologists can perform bedside evaluations such as assessing for muscle fatigability to establish a preliminary diagnosis without the need to await serologic testing or electromyography.¹⁵ Although serologic markers such as acetylcholine receptor (AChR) and muscle-specific kinase (MuSK) antibodies may support the diagnosis,^{16,17} their turnaround time may take weeks, limiting their applicability to acute decision-making.¹⁵ It is important to note that serologic markers may often be absent in patients with ICI-induced MG and are not required for diagnosis, though they represent an area of future investigation and possibly further prognostication.

The management of irNAEs, including MG, is guided by the grade of irAE toxicity.^{9,18} For grade 1 nAEs, ICIs may be continued with close monitoring or held. For grade 2 neurotoxicities, ICIs are held and corticosteroid therapy, whether intravenous or oral, is initiated. Agents such as pyridostigmine, an acetylcholinesterase inhibitor, may be used in the management of grade 2 ICI MG; however, is less effective (62% compared to approximately 94% for classic MG).^{19,20} In grade 3 or 4 irAE, ICIs are permanently discontinued, and high-dose steroids such as intravenous methylprednisolone are initiated along with IVIG or plasmapheresis, with refractory cases requiring other immunosuppressive therapies.¹⁸ While thymectomy is the standard of care for classic MG, it is not a part of the current guidelines in the management of ICI MG.¹⁹ Given its rarity, clinical complexity, and high mortality, a multidisciplinary approach involving oncology, neurology, and cardiology in cases of myocarditis are essential to improve patient outcomes.^{15,16}

CONCLUSION

ICI-induced MG is a well-documented, but life-threatening nAE, especially in the presence of overlapping syndromes such as concurrent myositis or myocarditis. Its high mortality rate necessitates early recognition, prompt neurologic consultation, respiratory monitoring in the critical care setting, and timely initiation of immunosuppressive therapy. A multidisciplinary approach can improve patient outcomes and potentially improve survival.

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