Myasthenia Gravis: A Rare Neurologic Complication of Immune Checkpoint Inhibitor Therapy

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Authors' disclosures of conflicts of interest are found at the end of this article.

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https://doi.org/10.6004/jadpro.2022.13.2.6

Abstract

Myasthenia gravis is an autoimmune disorder affecting the neuromuscular junction, which is characterized by the production of autoimmune antibodies to acetylcholine or muscle-specific kinase receptors, causing an error in transmission of nerve impulses to various muscles. The hallmark of myasthenia gravis is "grave or serious" fluctuating muscle weakness. Ocular, respiratory, bulbar, and skeletal muscles are most commonly affected; therefore, patients often present with fatigable ptosis, blurry vision, diplopia, change in facial expression, dysphagia, dysarthria, dyspnea, and limb weakness. Many medications, including fluroquinolone, aminoglycoside, magnesium sulfate, quinidine, and select beta blockers, are known to unmask or exacerbate symptoms of myasthenia gravis. Although the pathogenesis is not entirely understood, T lymphocytes are thought to play a role by blocking the acetylcholine receptors and causing antibody production. In the era of new immune-modulating therapies emerging for treatment of different cancers, their role in inducing a proinflammatory state has become apparent, thus highlighting a clear need to increase awareness about their role in inducing myasthenia gravis or myasthenia-like symptoms.

CASE STUDIES

A 64-year-old female with a history of hypertension, hypothyroidism, irritable bowel syndrome, and cutaneous malignant melanoma was started on treatment with a combination of ipilimumab (Yervoy) and nivolumab (Opdivo). Eight days after her first infusion of ipilimumab and nivolumab, she developed a cutaneous rash and bilateral uveitis, both treated with topical steroids. Shortly after, she presented to the emergency department with a new onset fatigable right eyelid ptosis, diplopia, and markedly elevated hepatic and muscle enzymes. A neurologic evaluation revealed elevated muscle-specific tyrosine kinase (MuSK) antibodies in the setting of an otherwise unremarkable workup, including a brain MRI, pulmonary

J Adv Pract Oncol 2022;13(2):151–157

function test, electromyography (EMG), and cerebral spinal fluid serology. She was diagnosed with immune checkpoint inhibitor (ICI)-induced ocular myasthenia gravis (MG) and was treated with pulse doses of glucocorticoids and pyridostigmine, with subsequent improvement in ocular symptoms. Combination therapy with ICI was permanently discontinued. After the resolution of her myasthenia symptoms and under close observation of a neurologist, she received single-agent pembrolizumab (Keytruda) for a total of four doses with subsequent regression of her primary tumor and no further exacerbation in myasthenia.

An 80-year-old man with a history of hypertension, dyslipidemia, remote history of prostate and renal cancers, and newly diagnosed metastatic malignant melanoma was initiated treatment with nivolumab monotherapy. Fourteen days after his first infusion, he was admitted to the hospital with complaints of progressive fatigue, proximal weakness in bilateral lower extremities, fatigable upward gaze with associated bilateral ptosis, and head drop. His workup revealed markedly elevated liver enzymes and striated muscle antibodies. Acetylcholine antibodies, central nervous system imaging, spinal fluid serology, and a pulmonary function test were unrevealing. The patient was treated with pulse doses of methylprednisolone, intravenous immunoglobulin (IVIG), and pyridostigmine, which was ultimately cross tapered to prednisone. After a prolonged hospitalization and delayed recovery, he was discharged home and continued oral steroids. Nivolumab was permanently discontinued. His cancer treatment options were subsequently limited to cytotoxic chemotherapy. The patient died shortly thereafter due to progressive disease.

A 70-year-old man with a history of non-insulin-dependent diabetes mellitus, remote history of colorectal cancer, and newly diagnosed hepatocellular carcinoma was treated with pembrolizumab. Following the second infusion of the ICI, he was admitted to the hospital for management of myocarditis requiring immunosuppressive therapy with high doses of intravenous steroids and percutaneous pacemaker placement. He stayed in the hospital for several weeks. Shortly after discharge, he was readmitted for a subacute worsening of dyspnea, hypophonia, dysarthria, and dysphagia requiring nasogastric tube placement for enteral nutrition support. On clinical evaluation, he was found to have mild bilateral ptosis, pronounced weakness of proximal lower limbs, and markedly elevated creatine phosphokinase level (CPK). Additional evaluation with a pulmonary function test revealed reduced total vital capacity and negative inspiratory pressure. A myasthenia antibody panel was obtained and demonstrated elevated binding, blocking, and modulating acetylcholine receptor (AChR) antibodies. Brain imaging, EMG, and cerebrospinal fluid serology were unrevealing. He received pulse dose glucocorticoids, pyridostigmine, IVIG, and subsequently plasma exchange, with no improvement in myasthenia symptoms. His hospital course was complicated by a thromboembolic event leading to hypercarbic respiratory failure, adrenal insufficiency, and sepsis. The patient subsequently died of complications of MG.

The immune system can mount innate and adaptive immune responses against different antigens, including malignant cells. CD4 and CD8 lymphocytes and natural killer (NK) cells are traditionally referred to as cytotoxic T cells. Their production is upregulated by the proinflammatory cytokines such as immunoglobulins, interleukins, and interferons. CD4 and CD8 lymphocytes initiate distinction between "self" and "non-self" antigens and are responsible for the specificity of T cells for a particular antigen. Unlike CD4 and CD8 lymphocytes, NK cells do not require antigen presentation for cytotoxic activity. NK cells express various killer immunoglobulin-like receptors and inhibitory molecules, including cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1). The effector function of CD4, CD8 lymphocytes, and NK cells enables the immune system to mount innate and adaptive immune responses against antigens. In contrast, T-regulatory cells largely inhibit cytotoxic T-lymphocyte activ-

ity, thus restoring immune homeostasis, or equilibrium. In patients with active cancer, cancer antigens overcome adaptive immune responses to produce an immune-tolerant environment. This mechanism, known as immunologic escape, allows cancer cells to propagate (Hottinger, 2016).

MECHANISM OF ACTION OF IMMUNE CHECKPOINT INHIBITORS

Immune checkpoint inhibitors function by restoring immune function against cancer antigens. CTLA-4 and PD-1 are two immune checkpoint proteins that are crucial for maintaining homeostasis. The binding of these checkpoint proteins to their ligands (CTLA-4 to CD80 or CD86 and PD-1 to PD-L1) results in the suppression of T-cell activation and downregulation of autoimmune responses by inhibiting effector T-cell proliferation and cytokine release (National Comprehensive Cancer Network, 2021). Monoclonal antibodies against CTLA-4 and PD-1 proteins block the receptor-ligand interaction and facilitate T-cell activation by inducing the demise of T-regulatory cells and upregulating production of T-effector cells. Additionally, CTLA-4 and PD-1 blockade induces cytokine production, which facilitates further proliferation of T cells (Ramos-Casals et al., 2020). By altering the ratio of T-regulatory to T-effector cells, ICIs facilitate an autoimmune response against tumor antigen.

The use of ICIs, such as pembrolizumab (Keytruda), nivolumab (Opdivo), durvalumab (Imfinzi), ipilimumab (Yervoy), and others, has transformed cancer care in recent years by offering significant improvement in overall and progression-free survival in certain cancers. Their benefit, however, should be weighed in the context of the potential immune-mediated toxicities that result from the overactivation of the immune system against any organ system. More common immune-related adverse events (irAEs) are well described in available literature; however, rare, but serious neurologic events, including encephalitis, aseptic meningitis, and myasthenia gravis (MG), cannot be overlooked (Suzuki et al., 2017).

ETIOLOGY

Myasthenia gravis is the most common disorder of neuromuscular transmission and is best categorized as an autoimmune disorder. Although the etiology of MG is not clearly understood, T lymphocytes are thought to be responsible for binding to acetylcholine receptors and stimulating antibody production. In a somewhat similar fashion, blockade of CTLA-4 and PD-1 immune checkpoint pathways is thought to produce an exaggerated autoimmune response directed at acetylcholine receptors or receptor-associated proteins. Cases of MG associated with ICIs were described by Makarious and colleagues (2017): Out of 23 reported cases, 72.7% were de novo MG, 18.2% were exacerbation of preexisting MG, and 9.1% were exacerbations of subclinical MG. The onset of symptoms varied between 2 to 12 weeks of initial ICI dose. All cases were associated with high morbidity and mortality rates (Makarious et al., 2017). In a retrospective analysis performed by Santomasso and colleagues (2018), of 4,864 patients treated with ICIs, five cases of MG were identified. The incidence was more prevalent in men than in women, with a median age of onset of 72.6 years. The onset of symptoms varied between 12 to 28 days. All patients developed at least one other concurrent immune-mediated toxicity, including transaminitis, uveitis, myositis, and myocarditis. All five patients required prolonged hospitalization. Two out of the five suffered long-term sequelae of MG and died. Immune checkpoint inhibitor therapy was permanently discontinued in four out of five patients (Santomasso et al., 2018).

DIAGNOSIS

The evaluation of patients receiving ICIs who are experiencing new neurologic signs and symptoms should include workup for central nervous system involvement of their cancer, metabolic derangements, infections or associated myositis, pneumonitis, or myocarditis, depending on the presenting symptoms (Haanen et al., 2017). The diagnosis of MG is based on clinical presentation and serologic testing. The hallmark of MG is fluctuating weakness in ocular, bulbar, facial, neck, limb, and respiratory muscles. There are two clinical forms of MG: ocular and generalized. More than 50% of patients present with ocular symptoms, with generalized symptoms usually developing within 2 years of the diagnosis (Pelak & Quan, 2021).

Diagnostic workup is recommended for all patients with suspected MG regardless of the sever-

ity of the presenting symptoms (Table 1). The most reliable testing that aids in the confirmation of the diagnosis includes serologic testing for acetylcholine receptor (AChR) antibodies, muscle-specific tyrosine kinase (MuSK) antibodies, and low-density lipoprotein receptor-related protein 4 (LRP4) antibodies. It should be noted that some MG cases are seronegative. AChR antibodies are seen in 80% to 85% of all MG cases, whereas MuSK antibodies are present in only 8% of all cases and mostly in patients with generalized MG (Makarious et al., 2017). MuSK-positive MG is thought to have different pathogenesis than AChR-positive MG, which might explain the differences in treatment responses, specifically to acetylcholinesterase inhibition (Bird, 2021).

Other diagnostic modalities such as the ice pack test can be used in patients with pronounced ocular symptoms. This is based on the hypothesis that eyelid weakness improves with direct cooling of the muscle. Electrophysiologic conformation with repetitive nerve stimulation (RNS) and electromyography (EMG) could be used in patients presenting with weakness in skeletal muscles. Pulmonary function testing, including measurement of total vital capacity and maximum negative inspiratory pressure, could be helpful in identifying and monitoring patients with weakness involving respiratory muscles and differentiating MG from pneumonitis or myocarditis. Similarly, in patients with respiratory insufficiency and elevated muscle enzymes, additional evaluation with ECG, cardiac exam, troponin, and transthoracic echocardiogram is warranted to rule out a primary or concurrent cardiac etiology (Brahmer et al., 2018). Tensilon testing is no longer used due to concern over a cholinergic crisis, specifically in elderly patients or patients with cardiac disease or asthma (Naji & Owens, 2017).

MANAGEMENT

The goal of medical management in patients with MG is to reduce symptoms, support respiratory function, and minimize potential side effects of medications. Prompt consultation with a neurologist and the involvement of a multidisciplinary team is essential both for accurate diagnosis, as well as for the implementation of an appropriate, effective treatment plan.

Management of immune-mediated MG as outlined by the American Society of Clinical Oncology and National Comprehensive Cancer Network is based on the severity of the presenting symptoms defined by Common Terminology Criteria for Adverse Events (Table 2). Symptomatic patients are treated with oral anticholinesterase

Table 1. Diagnostic Workup for Suspected Myasthenia Gravis Based on ASCO and NCCN Guidelines

Symptom severity (CTCAE grade)[a]	Recommended assessment
Moderate symptoms (grade 2) and severe symptoms (grades 3 and 4)	• Check for ocular and proximal muscle fatigability • Serum AChR and anti-MuSK Ab • Consider LRP4 Ab if AChR Ab are negative • PFT with NIF and VC • If suspected superimposed myositis, check CPK, ESR, CRP, aldolase • If abnormal PFT, elevated CPK, or suspected myocarditis, check troponin, ECG, TTE • Neurology consultation • Daily neurologic evaluation for patients presenting with grades 3 and 4 • MRI brain and/or spine depending on presenting symptoms • Electrodiagnostic studies[b] • Ice pack test[c]

Note. CTCAE = Common Terminology Criteria for Adverse Events; AChR = acetylcholine receptor; anti-MuSK Ab = anti-muscle-specific kinase antibodies; LRP4 Ab = low-density lipoprotein receptor-related protein 4 antibodies; PFT = pulmonary function test; NIF = negative inspiratory force; VC = vital capacity; CPK = creatine phosphokinase; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; ECG = electrocardiogram; TTE = transthoracic echocardiogram; MG = myasthenia gravis.
[a]CTCAE v5.0 defines grade 1 MG as asymptomatic or mild symptoms; however, per ASCO guidelines, there is no grade 1 toxicity for MG.
[b]Electrodiagnostic studies include neuromuscular junction testing with repetitive stimulation (RNS), nerve conduction study (NCS) to exclude neuropathy, and needle EMG to evaluate for myositis (ASCO).
[c]Ice pack test could be helpful in patients presenting with bulbar symptoms.

Table 2. Management of Myasthenia Gravis Based on ASCO and NCCN Guidelines

Symptom severity (CTCAE grade)	Recommended management
Moderate symptoms (Grade 2)	• Hold ICIs; may resume in grade 2 patients ONLY if symptoms resolve[a] • Consider inpatient care[b] • Consult neurologist • Start pyridostigmine at 30 mg po 3 times a day and gradually increase to a maximum of 120 mg po 4 times a day as tolerated and based on symptoms • Start corticosteroids (prednisone 1–1.5 mg/kg po daily), wean as tolerated over 4–6 weeks (ASCO)[c] • Avoid medications that could worsen MG (Table 3)
Severe symptoms (Grade 3 and 4)	• Permanently discontinue ICIs • Inpatient care, consider ICU monitoring • Consult neurologist • Daily neurologic evaluation • Frequent pulmonary function assessment • Consider elective intubation • Start pyridostigmine at 30 mg po 3 times a day and gradually increase to a maximum of 120 mg po 4 times a day as tolerated and based on symptoms • Methylprednisolone 1–2 mg/kg/day, wean based on symptom improvement over 4–6 weeks[d] • If no improvement within 48–72 h, continue steroids and initiate IVIG 2 g/kg over 5 days or plasmapheresis for 5 days[e] • Avoid medications that can worsen MG (Table 3)

Note. ICI = immune checkpoint inhibitor; IVIG = intravenous immunoglobulin; MG = myasthenia gravis.
[a]ASCO guidelines based on recommendations provided by the Myasthenia Gravis Foundation of America allow to resume ICIs in patients with grade 2 toxicity after resolution of MG symptoms (ASCO). NCCN guidelines recommend to permanently discontinue ICIs for all grades of MG.
[b]NCCN guidelines recommend inpatient monitoring for patients with grade 2 toxicity. ASCO guidelines recommend inpatient monitoring for patients with grades 3–4 toxicity.
[c]NCCN guidelines recommend prednisone started at 20 mg daily and increased by 5 mg every 3–5 days to a target dose of 1 mg/kg/day not to exceed 100 mg daily.
[d]High-dose steroids > 2 mg/kg/day may exacerbate symptoms (NCCN).
[e]Additional immunosuppressants (cyclosporine, mycophenolate, rituximab) might be considered in steroid-refractory MG (NCCN, ESMO).

inhibitors such as pyridostigmine, which help to increase the amount of acetylcholine available at the neuromuscular junction. Patients should be observed for pyridostigmine overdose, which has been associated with worsening muscle weakness due to cholinergic crisis.

Chronic immunosuppressants, including glucocorticoids and nonsteroidal immunosuppressive agents (cyclophosphamide, cyclosporin, methotrexate, mycophenolate, rituximab, etc.) are frequently used to downregulate exacerbated autoimmune responses. Prednisone is the most commonly used corticosteroid; however, in patients with no improvement within 48 to 72 hours, pulse doses of methylprednisolone 1 to 2 mg/kg/day could also be used and tapered slowly over a course of 4 to 6 weeks as symptoms improve. Steroid doses over 2 mg/kg/day are not recommended as they may exacerbate symptoms (NCCN, 2021). In more severe cases of MG where rapid immunomodulating treatment is necessary, short-acting intravenous immunoglobulin and plasma exchange are recommended (NCCN, 2021). Avoidance of drugs that may exacerbate symptoms of myasthenia and that can potentiate myasthenia crisis, including aminoglycosides, fluoroquinolones, magnesium, certain beta blockers, and neuromuscular blocking agents, is essential (Table 3). Elective intubation may be necessary in patients with reduction in forced vital capacity below 15 to 20 mL/kg and negative inspiratory pressure less than –25 to –30 cmH_2O or with worsening bulbar symptoms (Bird & Levine, 2021).

DISCUSSION

Over the past decade, the use of ICI therapy has changed the landscape of cancer treatment by improving progression-free and overall survival in many cancer types as compared with traditional cytotoxic chemotherapy. With an increased ability

Table 3. Examples of Drugs That May Worsen Myasthenia Gravis Symptoms and Potentiate Myasthenia Gravis Crisis

Antibiotics	*Cardiac agents*
Aminoglycosides	Beta blockers
Gentamicin	Atenolol
Amikacin	Labetalol
Tobramycin	Metoprolol
Neomycin	Propranolol
Streptomycin	Antiarrhythmic
Macrolides	Procainamide
Azithromycin	Quinidine
Erythromycin	*Neuromuscular blocking agents*
Clarithromycin	Succinylcholine
Fluoroquinolones	Pancuronium
Levofloxacin	Atracurium
Ciprofloxacin	Vecuronium
Ofloxacin	*Immune checkpoint inhibitors*
Moxifloxacin	Ipilimumab
Gemifloxacin	Nivolumab
Tetracyclines	Pembrolizumab
Minocycline	Durvalumab
Doxycycline	Atezolizumab
Tigecycline	*Other drugs*
	Magnesium
	Chloroquine

to manipulate and upregulate immune-mediated responses against cancer antigens, the need to better understand, anticipate and treat immune-mediated toxicities is emerging (Malani et al., 2017). Although the incidence of de novo and exacerbation of clinical and subclinical MG is relatively rare, all reported cases were associated with high in-hospital morbidity and mortality due to concurrent irAEs, sequalae of myasthenia, or acquired hospital complications. Additionally, with the continued increase in use of ICIs and increased awareness of potential neurologic irAEs, the incidence and recognition of immune-mediated MG is likely to rise.

Advanced practitioners (APs) working with oncology patient populations are uniquely positioned to recognize and promptly address early signs and symptoms of MG in patients treated with ICI. By providing thorough patient and caregiver education and performing meticulous follow-up, APs can facilitate early recognition of signs and symptoms of de novo or exacerbation of MG, initiate appropriate workup, and make prompt referral to a specialist for diagnosis and careful symptom management. Involvement of a multidisciplinary team, including neurologists, respiratory therapists, physical and occupational therapists, pharmacists, mental health professionals, and nurses is essential to support patients through treatment and recovery of ICI-related MG.

For patients with confirmed de novo ICI-related MG or exacerbation of preexisting MG, discontinuation or interruption of ICI therapy, avoidance of medications that might precipitate the development of MG or cholinergic crisis, along with careful monitoring of patients' clinical symptoms and respiratory status may prevent long-term sequelae of MG, and reduce morbidity and mortality rates, and hospital length of stay. There is some disagreement in the literature regarding rechallenge with ICI in patients with moderate MG that is fully resolved (NCCN, 2021; Brahmer et al., 2018). This highlights the need for careful consideration of risk and benefit, as well as shared decision-making with the patient. Close neurologic monitoring and follow-up is essential, especially for patients in whom challenge with ICI therapy is being considered. ●

Disclosure

The authors have no conflicts of interest to disclose.

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