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Benjamin Jinsung Park, Aaron W. Warning & Sruti S. Akella

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CASE REPORT



Checkpoint inhibitor-related myasthenia-myocarditis-myositis overlap syndrome in the orbit

Benjamin Jinsung Park, Aaron W. Warning, and Sruti S. Akella

Department of Ophthalmology and Visual Science, The Ohio State University Wexner Medical Center and The Ohio State University Comprehensive Cancer Center – James Cancer Center and Solove Research Institute, Columbus, Ohio, USA

ABSTRACT

We report a series of three patients who developed checkpoint inhibitor-related myocarditis with orbital myositis and/or myasthenia gravis overlap syndrome, with varying degrees of severity. In all cases, checkpoint inhibitor therapy was immediately discontinued upon diagnosis and corticosteroids were initiated. While two patients achieved substantial recovery, one patient passed away on hospital day three. These cases underscore the critical need for prompt recognition of adverse events associated with immune checkpoint inhibitors.

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Introduction

In recent decades, the introduction of immune checkpoint inhibitors (ICIs) has revolutionized cancer management. By blocking checkpoint proteins, these drugs enable the increased activation of the immune system, which may lead to death of cancer cells. The first ICI to gain approval by the Food and Drug Administration (FDA) was ipilimumab in 2011, which targets the cytotoxic T-lymphocyte antigen 4 (CTLA-4) and prevents inhibition of cytotoxic T cells.¹ Since that time, several other ICIs including pembrolizumab, nivolumab, and atezolizumab have also achieved regulatory approval for the management of various malignancies including lung cancer, bladder cancer, metastatic melanoma, and Hodgkin's lymphoma.^{2–4}

While immune checkpoint inhibitors have successfully expanded the oncologist's repertoire, they are not without risks. The enhanced activation of the immune system and increased cytotoxic activity can lead to inflammatory side effects known as immune-related adverse events (irAEs).⁵ These irAEs can range from mild to severe, most commonly affecting the skin, gastrointestinal tract, liver, and lung though any organ system can be involved.⁶ Due to the diverse nature of these irAEs, their evaluation and management often necessitate a multidisciplinary approach.

There is an emerging body of literature characterizing specifically the ophthalmic irAEs associated with ICI

therapy. Studies have reported the rate of ophthalmic irAEs as ranging from 0.2% to 4% depending on the ICI used, with the combination regimen of ipilimumab/nivolumab having the highest reported frequency.⁷ The most commonly reported ophthalmic irAEs include dry eye syndrome, conjunctivitis, and uveitis, although more morbid adverse events including optic neuropathy, retinal detachment, and myasthenia gravis-like syndrome have also been documented.⁸

Herein, we present three cases of orbital myositis overlap syndrome with symptom onset in the days to weeks following initiation of immune checkpoint inhibitor therapy. This case series was conducted in accordance with the ethical standard detailed in the Declaration of Helsinki and in compliance with the Health Insurance Portability and Accountability Act. Written consent was obtained from all patients or their legally appropriate representative.

Case presentations

Case 1

A 79-year-old female with a history of chronic myelogenous leukemia on imatinib and metastatic renal cell carcinoma on combination cabozantinib/nivolumab presented to the hospital with a four-week history of gradual-onset ptosis and diplopia. She had received her third cycle of nivolumab prior to symptom onset.

On exam, the patient's visual acuity, pupillary reaction, intraocular pressure, and color vision were intact. However, she was found to have bilateral ptosis with MRD1 of 0 mm in the right eye and -1.5 mm in the left eye, with levator function of 11 mm and 7 mm in each eye, respectively. There were also variable extraocular muscle (EOM) limitations in all directions of gaze in both eyes (Figure 1A). Her anterior segment exam was notable only for bilateral chemosis; her posterior segment exam was unremarkable. The patient's neurological exam was intact. MRI of the orbits with contrast revealed diffuse edema and patchy enhancement of all bilateral extraocular muscles and intraconal space, but no enhancement of the optic nerves (Figure 1B).

Serologic work-up for checkpoint inhibitor-related organ toxicity revealed elevated cardiac troponins and creatine kinase levels; a subsequent echocardiogram was unremarkable. A myasthenia gravis panel was negative. The patient was diagnosed with checkpoint inhibitor-related myositis and myocarditis, prompting immediate cessation of nivolumab and initiation of oral prednisone 1 mg/kg daily tapered over six weeks. Her ptosis, diplopia, and ophthalmoplegia gradually improved (Figure 1C) with near-complete resolution by 21 weeks.

Case 2

A 62-year-old male with a history of mesothelioma metastatic to the peritoneum was admitted for evaluation of rapid-onset diplopia, dyspnea, and generalized muscle weakness which started two weeks after his first infusion with combination ipilimumab and nivolumab.

On presentation, the patient's visual acuity, pupillary reaction, intraocular pressure, and color vision were intact. However, he had severe bilateral ptosis with a margin-reflex-distance 1 (MRD1) of -2 mm OU and a diminished levator function of 11 mm OU. In addition, there were variable motility limitations in all directions of gaze (Figure 2A). Anterior segment and dilated fundus exams were otherwise unremarkable. Neurologic examination indicated weakness in the bilateral upper and lower extremities, as well as absent lower extremity reflexes. Magnetic resonance imaging (MRI) of the orbits with contrast demonstrated patchy enhancement and inflammation of all extraocular muscles (Figure 2B) without enhancement of the optic nerves.

Suspecting checkpoint inhibitor-related toxicity, other organ biomarkers were obtained. Cardiac troponins, creatine kinase levels, and alanine transaminase (AST) and aspartate aminotransferase (ALT) levels were all elevated to at least two times the upper limits of normal. Myasthenia antibodies were negative; however, the

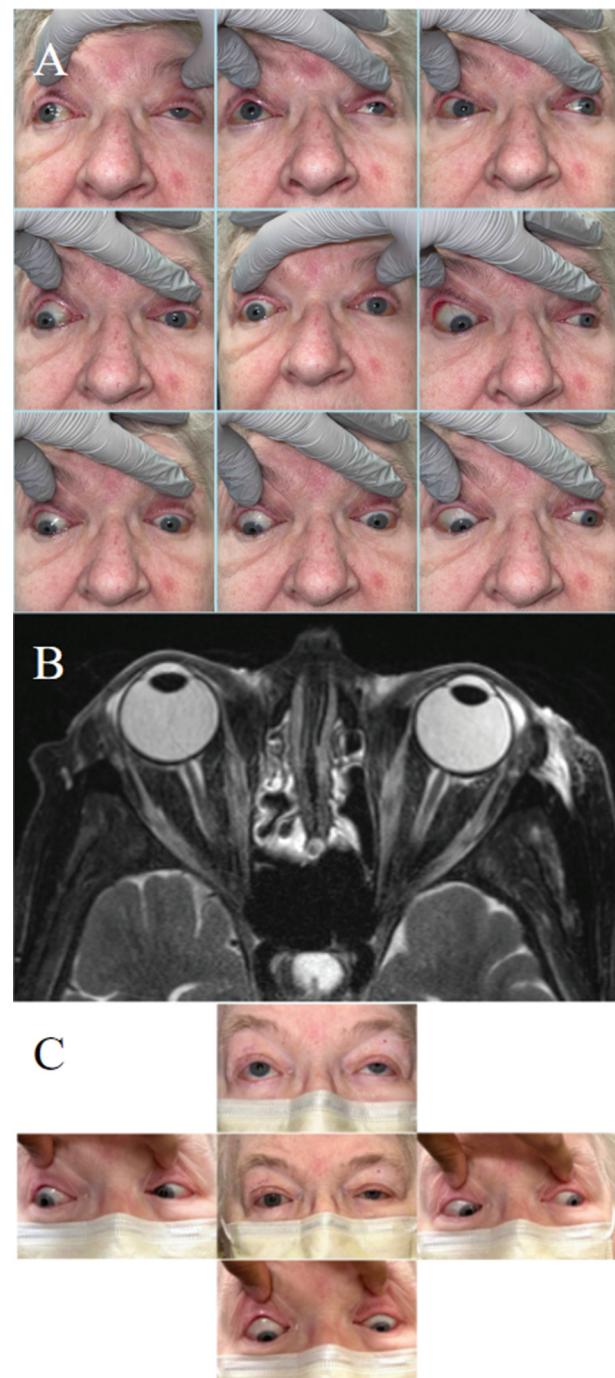


Figure 1. External photographs at presentation (A) show bilateral limitations in all directions of gaze. Axial T2-weighted MRI orbits with contrast (B) shows patchy hyperintensity and edema within the bilateral extraocular muscles. External photographs at 11 week follow up (C) show improvement in gazes.

Neurology service felt that a diagnosis of myositis alone did not explain the patient's areflexia. He was ultimately diagnosed with ICI-related myositis and myasthenic syndrome in addition to myocarditis and hepatitis.

Immunotherapy was immediately held and he was initiated on a combination of intravenous



Figure 2. External photographs at presentation (A) show ptosis (central image) and bilateral limitations in all directions of gaze. Axial T2-weighted MRI orbits with contrast (B) shows subtle patchy hyperintensity and edema within the bilateral extraocular muscles. External photographs at 18 week follow up (C) show improvement in ptosis and gazes.

methylprednisolone 2 mg/kg for 14 days followed by methylprednisolone 1 mg/kg for 7 additional days; intravenous immunoglobulin (IVIG) 400 mg for 6 doses; nine days of plasmapheresis; and oral pyridostigmine for myasthenic syndrome. After 26 days he was well enough to be discharged but was continued on an

outpatient regimen of weekly IVIG infusions, mycophenolate mofetil, pyridostigmine, and oral prednisone.

At follow-up he continued to exhibit gradual improvement in ptosis and ophthalmoplegia, with near-complete resolution at 18 weeks after cessation of checkpoint inhibitor therapy (Figure 2C). Visual field testing remained full without evidence of optic neuritis. His other medications were also successfully weaned within three months of hospital discharge.

Case 3

A 76-year-old female with a history of metastatic non-small cell lung cancer on pembrolizumab presented with a history of rapid-onset bilateral ptosis and generalized weakness, starting one week after her last infusion.

At presentation, the patient's visual acuity, pupillary reaction, intraocular pressure, and color vision were found to be intact. However, her exam revealed severe bilateral ptosis with an MRD1 of -4 mm OU, levator function of 0 OU, and variable limitations in all directions of gaze (Figure 3). There was bilateral chemosis but the remainder of the ophthalmology exam was otherwise unremarkable. Neurological exam showed dysphagia, moderate facial and tongue weakness, muffled voice, and proximal muscle weakness, sufficient for a clinical diagnosis of myasthenia gravis.

Serologies revealed grossly elevated cardiac troponins, creatinine kinase levels, and transaminases. Myasthenia gravis and ganglioside antibody panels were negative. She was diagnosed with acute ICI-related myocarditis, myositis, hepatitis, and serology-negative myasthenia gravis and started immediately on intravenous methylprednisolone 1 gram daily, intravenous immunoglobulin, oral pyridostigmine, and mycophenolate mofetil.

On the third day of hospitalization, she experienced an episode of ventricular tachycardia and ultimately required emergent intubation. Two days later, she went into cardiac arrest and passed away despite resuscitation efforts.

Discussion

Immune checkpoint inhibitors (ICIs) have seen a substantial uptake in clinical research and practice since the FDA first approved ipilimumab in 2011. Then, just 1.54% of cancer patients were eligible for checkpoint inhibitor therapy. As of 2018, that number had risen to 43.63%.⁹ Currently, there are over 3,000 clinical trials examining the efficacy of checkpoint inhibitors for cancer treatments, which account for around two-thirds of all ongoing oncology trials.¹⁰



Figure 3. External photographs at presentation showed bilateral limitations in all directions of gaze.

As ICIs have become more frequently prescribed, reports of ICI-related adverse events have also risen and are now thought to affect anywhere from 54–76% of treated patients.¹¹ Ranging in severity from relatively benign to fatal, irAEs can affect virtually any organ system in the body, including the eye and orbit.^{12–20} These cases highlight the particular irAE of immune-related neuromuscular disorders, which primarily include myositis and immune-related myasthenia gravis (irMG), which is clinically distinct from classic myasthenia gravis (MG).²¹ For example, irMG tends to affect older men and does not require work-up for an underlying thymoma. irMG is also more likely to be seronegative: only 66.7% of patients are positive for anti-acetylcholine receptor antibodies, compared to 85–87% in classic MG. Furthermore, repetitive nerve stimulation testing is positive only 50% of the time as opposed to 60% for classic MG. Standard therapy for classic MG may also not be as effective for those with irMG. A review of 47 patients with irMG showed a mortality rate of 29.8%, whereas the mortality rate of classic MG is around 6%.²¹ Of note, in 2022 the

European Society for Medical Oncology published consensus guidelines for managing a distinct emerging entity now known as “immune-related-MG-like syndrome” (irMG-like), in which exercise-dependent fluctuating weakness of the proximal extremities or bulbar muscle groups and ocular symptoms such as ptosis and diplopia are seen.²² Approximately two-thirds of such patients are positive for anti-acetylcholine receptor antibodies, and early consultation with a Neurologist is mandatory.²²

Of particular interest is an increasingly recognized association of checkpoint inhibitor-related myocarditis with myositis and/or myasthenia gravis.²³ This triad is often referred to in the literature as “myasthenia-myocarditis-myositis” syndrome (MMM) or, perhaps more accurately, ICI-induced myocarditis with myositis and/or myasthenia gravis overlap syndrome (IM3OS), since the presentation of the myasthenia component is highly variable.^{23–28} In the largest review of cases to date of 60 people with IM3OS, the median age of onset was 71 years and the majority of patients (67%) were men, with melanoma being the most common underlying

malignancy. Pembrolizumab, nivolumab, and ipilimumab were the most common inciting ICIs, with 47 patients on single therapy and 13 on dual therapy (typically nivolumab with ipilimumab).²³ All 60 patients had ICI-induced myocarditis and myositis, but only 22 patients (37%) were diagnosed with concomitant myasthenia gravis. Common presenting signs including myalgia, proximal limb weakness, and fatigue, with most cases being rapidly progressive. Most patients developed symptoms within a median of one ICI dose, which correlates with the largest case series of ICI-associated myocarditis to-date (122 cases), where the median time from starting ICI therapy to presentation was 30 days, implying one or two doses prior to symptom onset.²⁹ The diagnosis of ICI-associated myocarditis alone is concerning, as it carries a reported mortality rate of up to 46%.²⁹ However, for cases of myocarditis with concomitant myasthenia-like symptoms, the reported mortality rate is even higher, at up to 62.5%,³⁰ and the largest review of cases of IM3OS had a mortality rate of 60%.²³

Thus, our cases highlight the wide spectrum of immune-related IM3OS as pertains to the orbit: Case #1 demonstrates only an isolated case of orbital myositis with mild accompanying myocarditis; Case #2 shows orbital myositis with myocarditis and concomitant immune-related-MG-like syndrome, in which a diagnosis of myositis alone did not explain all presenting neuromuscular symptoms, yet there was not sufficient clinical evidence to definitively make a diagnosis of myasthenia gravis; and Case #3 highlights a more classic presentation of IM3OS in which orbital myositis, myocarditis, and bulbar weakness consistent with serology-negative myasthenia gravis are seen. That serologies were negative in Case #3 reiterate a key distinction between irMG and classic MG, which is that irMG is more often seronegative.²¹

As our cases show, there is considerable overlap in these presentations, and a clear distinction of orbital myositis from immune-related-MG-like syndrome from immune-related-myasthenia gravis is not always possible.²² However, what is known is that it is essential for the ophthalmologist to recognize clinical signs of orbital myositis in patients on immune checkpoint inhibitors and to initiate workup for neurological and/or cardiovascular toxicity, which appear to be not infrequently associated with orbital myositis to varying degrees of severity.

When suspected, the evaluation of patients with a suspected IM3OS should include a comprehensive rheumatologic and neurologic review of systems and examination, laboratory testing (including troponins, CK, and aldolase to evaluate for myositis/myocarditis),

ECG, and echocardiogram. CK levels and inflammatory markers (ESR, CRP) can be used for monitoring disease activity. Autoantibody panels for myositis, myasthenia gravis, and paraneoplastic processes can be considered, although a negative result does not rule out the diagnosis. Some additional diagnostic tests that could prove useful include urinalysis, EMG, cardiac MRI, and tissue biopsy. Rheumatology and/or neurology consultations should be sought.

There is limited data to guide the treatment of IM3OS. According to expert consensus, management currently begins with “grading” the relevant irAEs according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.³¹ In general, Grade 1 irAEs can be managed with watchful waiting and ICI therapy may be continued. Patients with Grade 2 irAEs should temporarily halt ICI therapy and instead initiate treatment with corticosteroids (at least 0.5 mg/kg daily),^{23,30,32} which are then tapered over 4–8 weeks if symptoms stabilize. ICI may then be restarted at the conclusion of the taper if patients remain asymptomatic. However, if there is no response to corticosteroids, or if irAEs are deemed Grade 3–4, then a stepwise approach is used: ICI therapy is definitively discontinued, higher-dose corticosteroids (1–2 mg/kg daily) are given, and adjunctive therapies are considered on a case-by-case basis (e.g. tacrolimus, infliximab, mycophenolate mofetil, antithymocyte globulin, tocilizumab, abatacept, ruxolitinib, eculizumab, intravenous immunoglobulins (IVIG), and/or plasmapheresis).^{23,27,33} In practice, clinicians often initiate these therapies simultaneously depending on the severity of clinical presentation or abnormal serologies. For severe organ dysfunction, the patient should be admitted to an intensive care unit with supportive modalities available as needed such as intubation, pacemaker implantation, vasopressors, and even extracorporeal membrane oxygenation.^{21,24} It is important to recognize that presumed immune-related-MG-like syndrome or IM3OS are specifically considered high-grade irAEs for which immediate ICI cessation (owing to myocarditis), corticosteroids, and pyridostigmine are the first-line management approach.²² In most cases of immune-related myocarditis, ICI therapy is not restarted.²² This is consistent with the management of our cases and in direct contrast to prior reports, in which isolated ocular myositis without other organ system involvement may be successfully managed without stopping ICI therapy.^{13,18,19} A summary of management strategies is shown in Table 1.

This series of patients with IM3OS highlights the importance of recognizing that ophthalmic irAEs typically do not occur in isolation and should prompt a systemic workup. In milder cases where the myocarditis

Table 1. Grading of relevant irAEs according to the CTCAE v5.0³¹.

Diagnosis	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Myositis	Mild pain	Moderate pain associated with weakness; pain limiting instrumental ADL	Pain associated with severe weakness; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	–
Myasthenia gravis	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Myocarditis	–	Symptoms with moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms	Life-threatening consequences; urgent intervention indicated	Death

*ADL: activities of daily living.

component is asymptomatic and the orbital symptoms predominate, such as Case #1, the ophthalmologist may be the first consultant to evaluate the patient. Knowledge and prompt recognition of this entity is therefore essential to undertaking a timely systemic work-up and initiating the appropriate treatment. Although the paucity of existing literature precludes widespread generalizations, certain trends have been reported which should be kept in mind when evaluating any patient on checkpoint inhibitors: namely, irAEs typically present between 2–16 weeks after starting checkpoint inhibitors but do not have any known association with cumulative ICI dose; anti-CTLA-4 agents are more prone to irAEs compared to PD-1 inhibitors, with combination strategies increasing the incidence, onset, and severity of irAEs^{11,32}; and finally, irAEs can present with a wide range of severity and may herald fatal events.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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