

A Case Series of Rare Immune-Mediated Adverse Reactions at the New Mexico Veterans Affairs Medical Center

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Background: Immune checkpoint inhibitor (ICI) therapy has revolutionized the treatment of several solid tumors. The use of ICIs is expected to rise as a growing number of indications are approved for their use by the US Food and Drug Administration and with the increasing number of patients with cancer. Unfortunately, ICIs are associated with the development of immune-mediated adverse reactions (IMARs). About 5% to 10% of patients developing severe toxicities requiring treatment postponement or discontinuation. IMARs can affect any organ, but most frequently the skin and endocrine glands are involved.

Case Presentation: We present a case series of IMARs observed at the New Mexico Veterans Affairs Medical Center. First, we present a case of grade 4 myocarditis in an 84-year-old man receiving chemoimmunotherapy for lung

adenocarcinoma to demonstrate the rapid progression of this rare condition. Second, we present a case of uveitis in a 70-year-old man with superficial bladder cancer undergoing treatment with pembrolizumab. Finally, we present a case of a 63-year-old man with pleuritis and organizing pneumonia secondary to dual ICI treatment (nivolumab and ipilimumab) for mesothelioma. A discussion regarding the epidemiology of these IMARs, expected course, and optimal management follows each rare toxicity described.

Conclusions: Though these toxicities are uncommon, they serve as a reminder to clinicians across specialties that IMARs can drive the acute deterioration of any organ, and consideration of toxicities secondary to ICIs should be considered for any atypical presentation of unclear etiology.

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Immune checkpoint inhibitors (ICIs), often broadly referred to as immunotherapy, are being prescribed at increasing rates due to their effectiveness in treating a growing number of advanced solid tumors and hematologic malignancies.¹ It has been well established that T-cell signaling mechanisms designed to combat foreign pathogens have been involved in the mitigation of tumor proliferation.² This protective process can be supported or restricted by infection, medication, or mutations.

ICIs support T-cell-mediated destruction of tumor cells by inhibiting the mechanisms designed to limit autoimmunity, specifically the programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) pathways. The results have been impressive, leading to an expansive number of US Food and Drug Administration (FDA) approvals across a diverse set of malignancies. Consequently, the Nobel Prize in Physiology or Medicine was awarded for such work in 2018.³

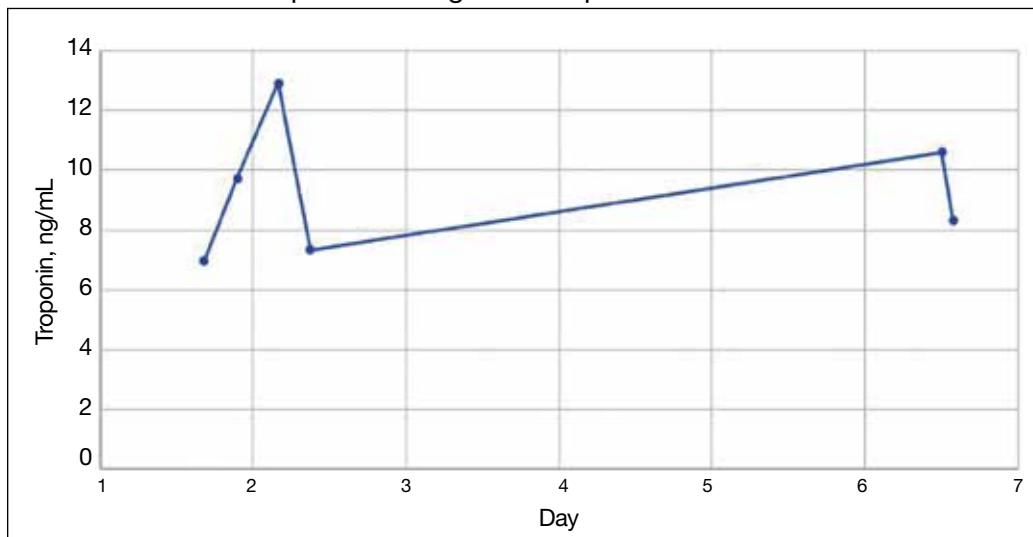
BACKGROUND

While altering these pathways has been shown to hinder tumor growth, the lesser restrictions on the immune system can drive unwanted au-

toimmune inflammation to host tissue. These toxicities are collectively known as immune-mediated adverse reactions (IMARs). Clinically and histologically, IMARs frequently manifest similarly to other autoimmune conditions and may affect any organ, including skin, liver, lungs, heart, intestine (small and large), kidneys, eyes, endocrine glands, and neurologic tissue.^{4,5} According to recent studies, as many as 20% to 30% of patients receiving a single ICI will experience at least 1 clinically significant IMAR, and about 13% are classified as severe; however, < 10% of patients will have their ICIs discontinued due to these reactions.⁶

Though infrequent, a thorough understanding of the severity of IMARs to ICIs is critical for the diagnosis and management of these organ-threatening and potentially life-threatening toxicities. With the growing use of these agents and more FDA approvals for dual checkpoint blockage (concurrent use of CTLA-4 and PD-1/PD-L1 inhibitors), the absolute number of IMARs is expected to rise, thereby leading to more exposure of such events to both oncology and nononcology clinicians. Prior literature has clearly described the treatments and outcomes for many common severe toxicities; however, information regarding presentations and outcomes for rare IMARs is lacking.⁷

FIGURE 1 Case 1: Troponin Throughout Hospitalization



A few fascinating cases of rare toxicities have been observed at the New Mexico Veterans Affairs Medical Center (NMVAMC) in Albuquerque despite its relatively small size compared with other US Department of Veterans Affairs medical centers. As such, herein, the diagnostic evaluation, treatments, and outcomes of rare IMARs are reported for each case, and the related literature is reviewed.

Patient Selection

Patients who were required to discontinue or postpone treatment with any ICI blocking the CTLA-4 (ipilimumab), PD-1 (pembrolizumab, nivolumab, cemiplimab), or PD-L1 (atezolizumab, avelumab, durvalumab) pathways between 2015 to 2021 due to toxicity at the NMVAMC were eligible for inclusion. The electronic health record was reviewed for each eligible case, and the patient demographics, disease characteristics, toxicities, and outcomes were documented for each patient. For the 57 patients who received ICIs within the chosen period, 11 required a treatment break or discontinuation. Of these, 3 cases were selected for reporting due to the rare IMARs observed. This study was approved by the NMVAMC Institutional Review Board.

CASE 1: MYOCARDITIS

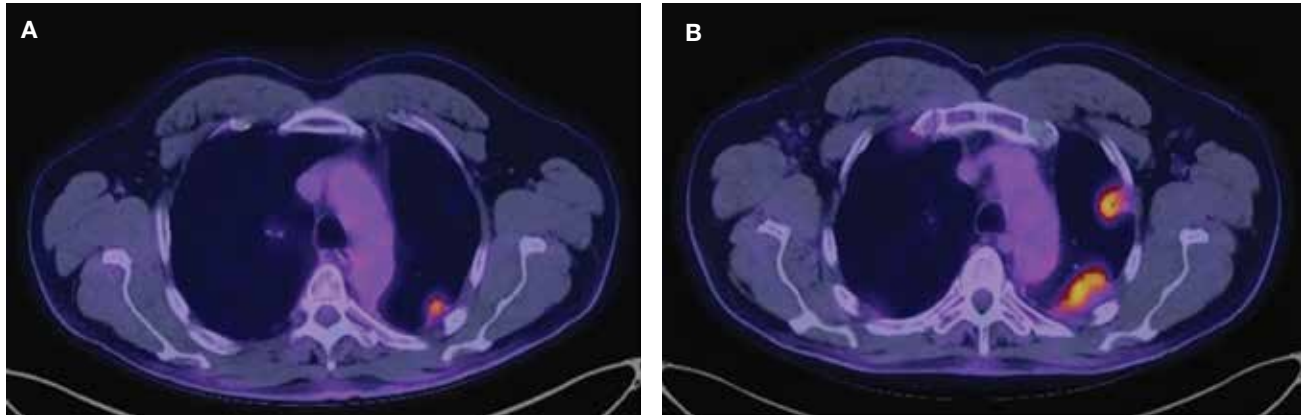
An 84-year-old man receiving a chemoimmunotherapy regimen consisting of carboplatin, pemetrexed, and pembrolizumab for recurrent, stage IV lung adenocarcinoma de-

veloped grade 4 cardiomyopathy, as defined by the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, during his treatment.⁸ He was treated for 2 cycles before he began experiencing an increase in liver enzymes. He then began developing chest pain and shortness of breath with a troponin increase to 13 ng/mL (Figure 1).

The patient's presentation was concerning for myocarditis, and he was quickly admitted to NMVAMC. Cardiac catheterization did not reveal any signs of coronary occlusive disease. Prednisone 1 mg/kg was administered immediately; however, given continued chest pain and volume overload, he was quickly transitioned to solumedrol 1000 mg IV daily. After the initiation of his treatment, the patient's transaminitis began to resolve, and troponin levels began to decrease; however, his symptoms continued to worsen, and his troponin rose again. By the fourth day of hospitalization, the patient was treated with infliximab, a tumor necrosis factor- α inhibitor shown to reverse ICI-induced autoimmune inflammation, with only mild improvement of his symptoms. The patient's condition continued to deteriorate, his troponin levels remained elevated, and his family decided to withhold additional treatment. The patient died shortly thereafter.

Discussion

Cardiotoxicity resulting from ICI therapy is far less common than the other potential severe

FIGURE 2 Case 3: Fluorodeoxyglucose-Positron Emission Tomography

A, Organizing pneumonia associated with immune checkpoint inhibitors while the patient was on ipilimumab and nivolumab can be seen. B, 2 months after discontinuing ipilimumab but continuing nivolumab.

toxicities associated with ICIs. Nevertheless, many cases of ICI-induced cardiac inflammation have been reported, and it has been widely established that patients treated with ICIs are generally at higher risk for acute coronary syndrome.⁹⁻¹¹ Acute cardiotoxicity secondary to autoimmune destruction of cardiac tissue includes myocarditis, pericarditis, and vasculitis, which may manifest with symptoms of heart failure and/or arrhythmia. Grading of ICI-induced cardiomyopathy has been defined by both CTCAE and the American Society of Clinical Oncology (ASCO), with grade 4 representing moderate to severe clinical decompensation requiring IV medications in the setting of life-threatening conditions.

Review articles have described the treatment options for severe cases.^{7,12} As detailed in prior reports, once ICI-induced cardiomyopathy is suspected, urgent admission and immediate evaluation to rule out acute coronary syndrome should be undertaken. Given the potential for deterioration despite the occasional insidious onset, aggressive cardiac monitoring, and close follow-up to measure response to interventions should be undertaken.

CASE 2: UVEITIS

A 70-year-old man who received pembrolizumab as a bladder-sparing approach for his superficial bladder cancer refractory to intravesical treatments developed uveitis. Approximately 3 months following the initiation of treatment, the patient reported bilateral itchy eyes, erythema, and tearing. He had a known history of allergic conjunctivitis that predated the ICI therapy, and consequently, it was un-

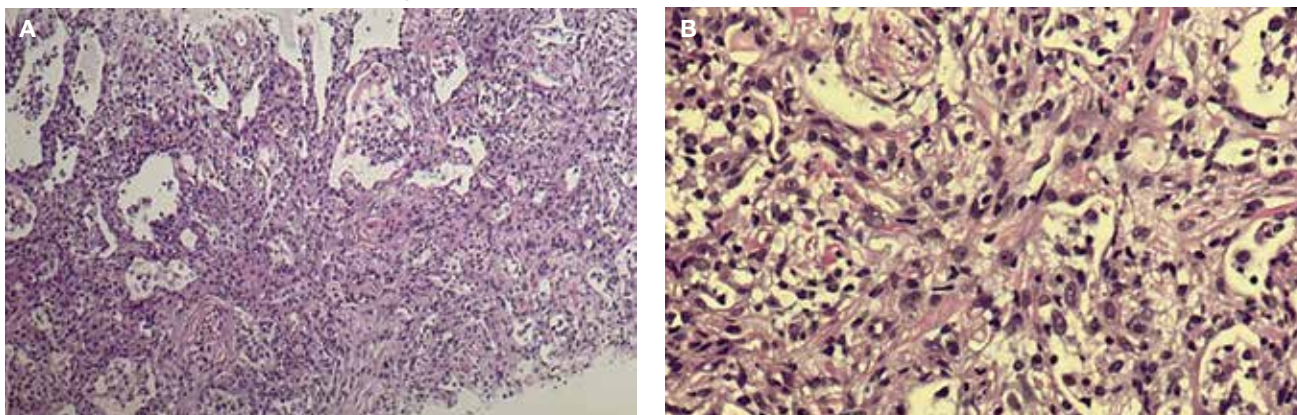
clear whether his symptoms were reflective of a more concerning issue. The patient's symptoms continued to wax and wane for a few months, prompting a referral to ophthalmology colleagues at NMVAMC.

Ophthalmology evaluation identified uveitic glaucoma in the setting of his underlying chronic glaucoma. Pembrolizumab was discontinued, and the patient was counseled on choosing either cystectomy or locoregional therapies if further tumors arose. However, within a few weeks of administering topical steroid drops, his symptoms markedly improved, and he wished to be restarted on pembrolizumab. His uveitis remained in remission, and he has been treated with pembrolizumab for more than 1 year since this episode. He has had no clear findings of superficial bladder cancer recurrence while receiving ICI therapy.

Discussion

Uveitis is a known complication of pembrolizumab, and it has been shown to occur in 1% of patients with this treatment.^{13,14} It should be noted that most of the studies of this IMAR occurred in patients with metastatic melanoma; therefore the rate of this condition in other patients is less understood. Overall, ocular IMARs secondary to anti-PD-1 and anti-PD-L1 therapies are rare.

The most common IMAR is surface ocular disease, consisting of dry eye disease (DED), conjunctivitis, uveitis, and keratitis. Of these, the most common ocular surface disease is DED, which occurred in 1% to 4% of patients treated with ICI therapy; most of these

FIGURE 3 Case 3: Photomicrograph of Pleural Biopsy

Results are consistent with organizing pneumonia due to immune checkpoint inhibitor therapy showing whorls of fibroblasts in a polypoid morphology obstructing alveolar spaces (A, low power; B, high power).

reactions are mild and self-limiting.¹⁵ Atezolizumab has the highest association with ocular inflammation and ipilimumab has the highest association with uveitis, with reported odds ratios of 18.89 and 10.54, respectively.¹⁶ Treatment of ICI-induced uveitis generally includes topical steroids and treatment discontinuation or break.¹⁷ Oral or IV steroids, infliximab, and procedural involvement may be considered in refractory cases or those initially presenting with marked vision loss. Close communication with ophthalmology colleagues to monitor visual acuity and ocular pressure multiple times weekly during the acute phase is required for treatment titration.

CASE 3: ORGANIZING PNEUMONIA

A man aged 63 years was diagnosed with malignant mesothelioma after incidentally noting a pleural effusion and thickening on routine low-dose computed tomography surveillance of pulmonary nodules. A biopsy was performed and was consistent with mesothelioma, and the patient was started on nivolumab (PD-1 inhibitor) and ipilimumab (CTLA-4 inhibitor). The patient was initiated on dual ICIs, and after 6 months of therapy, he had a promising complete response. However, after 9 months of therapy, he developed a new left upper lobe (LUL) pleural-based lesion (Figure 2A). This pleural nodule had limited standardized uptake value activity compared with the prior mesothelioma and was suspicious for some type of inflammatory process other than mesothelioma.

A biopsy was performed, and the histopathologic appearance was consistent with

organizing pneumonia (OP) (Figure 3). This was thought to be due to the patient's immunotherapy. Ipilimumab was quickly discontinued, and he was restarted on single-agent nivolumab following a prolonged break. However, he was then discovered to have increased LUL involvement after only 2 additional months of nivolumab monotherapy, which was also discontinued (Figure 2B). Another biopsy was undertaken to ensure the patient had no mesothelioma recurrence, and repeat histopathology confirmed OP progression. He was most recently treated with a prolonged steroid taper for OP and maintenance chemotherapy to reduce the likelihood of mesothelioma recurrence. The patient has remained asymptomatic despite the progression of his OP.

Discussion

ICIs can uncommonly drive pneumonitis, with the frequency adjusted based on the number of ICIs prescribed and the primary cancer involved. Across all cancers, up to 5% of patients treated with single-agent ICI therapy may experience pneumonitis, though often the findings may simply be radiographic without symptoms. Moreover, up to 10% of patients undergoing treatment for pulmonary cancer or those with dual ICI treatment regimens experience radiographic and/or clinical pneumonitis.¹⁸ The clinical manifestations include a broad spectrum of respiratory symptoms. Given the convoluting concerns of cancer progression and infection, a biopsy is often obtained. Histopathologic findings of pneumonitis may include diffuse alveolar damage

and/or interstitial lung disease, with OP being a rare variant of ILD.

Among pulmonologists, OP is felt to have polymorphous imaging findings, and biopsy is required to confirm histology; however, histopathology cannot define etiology, and consequently, OP is somewhat of an umbrella diagnosis. The condition can be cryptogenic (idiopathic) or secondary to a multitude of conditions (infection, drug toxicity, or systemic disease). It is classically described as polypoid aggregations of fibroblasts that obstruct the alveolar spaces.¹⁹ This histopathologic pattern was demonstrated in our patient's lung biopsy. Given a prior case description of ICIs, mesothelioma, OP development, and the unremarkable infectious workup, we felt that the patient's OP was driven by his dual ICI therapy, thereby leading to the ultimate discontinuation of his ICIs and initiation of steroids.²⁰ Thankfully, the patient had already obtained a complete response to his ICIs, and hopefully, he can attain a durable remission with the addition of maintenance chemotherapy.

CONCLUSIONS

ICIs have revolutionized the treatment of a myriad of solid tumors and hematologic malignancies, and their use internationally is expected to increase. With the alteration in immunology pathways, clinicians in all fields will need to be familiarized with IMARs secondary to these agents, including rare subtypes. In addition, the variability in presentations relative to the patients' treatment course was significant (between 2-9 months), and this highlights that these IMARs can occur at any time point and clinicians should be ever vigilant to spot symptoms in their patients.

It was unexpected for the 3 aforementioned rare toxicities to arise at NMVAMC among only 57 treated patients, and we speculate that these findings may have been observed for 1 of 3 reasons. First, caring for 3 patients with this collection of rare toxicities may have been due to chance. Second, though there is sparse literature studying the topic, the regional environment, including sunlight exposure and air quality, may play a role in the development of one or all of these rare toxicities. Third, rates of these toxicities may be underreported in the literature or attributed to other conditions rather than due to ICIs at other sites, and the uncommon nature of

these IMARs may be overstated. Investigations evaluating rates of toxicities, including those traditionally uncommonly seen, based on regional location should be conducted before any further conclusions are drawn.

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Ethics and consent

No informed consent was obtained from the patients; patient identifiers were removed to protect the patient's identity.

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