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Case Report

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Immune-Related Myocarditis Presenting as Shortness of Breath and Complete Heart Block in an Urothelial Cancer Patient Receiving Pembrolizumab: A Case Report

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Abstract

Pembrolizumab is an immune-checkpoint inhibitor (ICI) drug approved for the treatment of patients who have locally advanced or metastatic urothelial cancer and are not eligible for cisplatin-containing therapy. However, like other anti-PD-1s, pembrolizumab can cause immune- related adverse events (irAEs), some of which can be serious enough to warrant emergency care 3-7. Pembrolizumab-related cardiac irAEs, owing to the increased morbidity and mortality associated with them, can present a special challenge in the emergency department. Most documented cardiac irAEs occurred in patients receiving anti-PD-1s in combination with other agents or in patients with pre-existing heart conditions and were easily resolved with steroid treatment8. Herein, we describe a case with unclear symptom presentation in a patient with no previous cardiac history receiving only 1 dose of pembrolizumab. Knowledge gained from this case and others will help elucidate the early- and late-onset toxic effects associated with pembrolizumab and inform the development of effective algorithms for the identification and management of these effects, thereby optimizing the safety of pembrolizumab and other immunotherapy agents in the Emergency Department.

Introduction

Pembrolizumab, a humanized monoclonal IgG4 antibody targeting programmed cell death protein 1 (PD-1), has been shown to increase the overall survival rates of patients with a variety of malignancies. This immune-checkpoint inhibitor (ICI) drug is now approved for the treatment of patients who have locally advanced or metastatic urothelial cancer and are not eligible for cisplatin-containing therapy [1, 2]. However, like other anti-PD-1s, pembrolizumab can cause immune-related adverse events (irAEs), some of which can be serious enough to warrant emergency care [3-7]. The prompt and effective management of these irAEs requires the early recognition of signs and symptoms of potential relevance.

Most pembrolizumab-related irAEs, including fatigue, rash, pruritus, arthralgia, and diarrhea, are usually mild and self-limiting [6]. In contrast, pembrolizumab-related cardiac irAEs, owing to the increased morbidity and mortality associated with them, can present a special challenge in the emergency department. Most documented cardiac irAEs occurred in patients receiving anti-PD-1s in combination with other agents or in patients with pre-existing heart conditions and were easily resolved with steroid treatment [8]. Herein, we describe a case with unclear symptom presentation in a patient with no previous cardiac history receiving only 1 dose of pembrolizumab. Knowledge gained from this case and others will help elucidate the early- and late-onset toxic effects associated with pembrolizumab and inform the development of effective algorithms for the identification and management of these effects, thereby optimizing the safety and efficacy of pembrolizumab.

Case Report

A 70-year-old man with a history of metastatic urothelial cancer presented to the emergency department with complaints of vision changes, fatigue, and right eye ptosis. Five months earlier, the patient had been diagnosed with bladder cancer, for which he underwent surgery and received 6 cycles of chemotherapy consisting of cisplatin, gemcitabine, and ifosfamide. Two weeks before presentation, he received his first dose of pembrolizumab after metastases had been discovered. Aside from mild renal insufficiency, the patient had no other medical conditions.

The patient reported that 12 days after receiving pembrolizumab, he started having difficulty moving his right eye, shortness of breath, and mild pain in his left trapezius and right calf muscles. At presentation, the patient had a heart rate of 52 bpm, blood pressure of 108/63 mmHg, room air oxygen saturation of 96%, and temperature of 36°C. Non-contrast-enhanced computed tomography of the head was negative; 2-view chest x-ray showed features consistent with atelectasis. The patient had markedly elevated levels of cardiac enzymes, including creatine kinase (12,706 U/L), troponin T (2,740 ng/L), and creatine kinase muscle/blood (272.3 ng/mL); an

elevated white blood cell count (13.8 K/uL); elevated levels of the liver enzymes aspartate aminotransferase (240 U/L) and alanine aminotransferase (591 U/L); and a creatinine level of 1.96 mg/dL, up from 1.76 mg/dL 2 weeks previously. Owing to concerns about irAEs, the patient was given intravenous methylprednisolone (1 mg/kg) and admitted for further workup.

Approximately 8 hours after initial presentation, the patient had bradycardia with a heart rate of 30-39 bpm. Electrocardiography revealed third-degree atrioventricular block. Transcutaneous pacing was attempted and resulted in the patient feeling nauseated and vomiting, although his shortness of breath did not worsen and he had good mentation. The patient was started on intravenous dopamine and transferred to the intensive care unit (ICU), where he continued receiving intravenous dopamine and remained alert and oriented overnight.

On day 2, a transvenous pacemaker was placed. The patient's laboratory tests revealed worsening renal function, increasing cardiac enzyme levels, and thyroiditis. The patient received plasmapheresis and continued intravenous methylprednisolone. Owing to an increased shortness of breath, the patient also initiated bilevel positive airway pressure. On day 3, he was electively intubated because he required a high amount of oxygen (80-90%). Blood gas assessment with bi-level positive airway pressure at 50% revealed an arterial pH of 7.38/29/140/17/-7/100%; the patient's respiratory rate was 40-50 breaths/minute. On day 4, the patient continued to have progressive oliguric renal failure with a creatinine level of 3.5 mg/dL. The patient continued to have hypotension requiring 2 vasopressors and intravenous antibiotics. Owing to concerns about aspiration pneumonia, an infectious disease consult was requested. On day 5, the patient's troponin level was 7008 U/L, and echocardiography showed biventricular failure along with signs and symptoms of congestive heart failure. He was given 1 dose of infliximab. On day 6, the patient was on 3 vasopressors (vasopressin, norepinephrine, and phenylephrine), and his cardiac rhythm was unstable and included wide complex tachycardia and ischemic ST-T changes. His creatine kinase level was 584 U/L; his troponin-T level, 11,070 ng/L; and creatine kinase- muscle/brain level, 99.3 ng/mL. That afternoon, the patient became hypotensive again and had cardiopulmonary arrest twice shortly thereafter. He died about 3 hours later.

Discussion

This case is a prime example of how irAE presentation may not be straightforward. Studies suggest that irAEs can affect almost any organ [9, 10]. The rates and types of irAEs vary depending on the involved organ, ICI class, and tumor type [11-13]. The occurrence of irAEs may not follow a cyclical pattern as seen with cytotoxic chemotherapy. Emergency medicine physicians must recognize that irAE symptoms can occur at any time during the disease trajectory and can involve multiple organ systems. Taking a broader history and comprehensively reviewing organ systems during initial workup, as in our case, may help uncover irAEs. Therefore, when irAEs are suspected, it is prudent to order a wide range of laboratory tests to assess the function of multiple organ systems. Emergency medicine physicians are taught to order laboratory tests parsimoniously; however, owing to the unique way in which
irAEs present, patients with suspected irAEs, even if they are asymptomatic in certain organ systems, should have a broader routine workup that includes liver function tests, a complete blood count, a comprehensive metabolic panel, and assessments of thyroid stimulating hormone, creatine kinase, and brain natriuretic peptide levels.

Myocarditis in patients receiving ICIs is rare. In one study, the myocarditis rate was 0.09% for patients receiving a single ICI and 0.27% for patients receiving combination therapy; in another study, 1% of patients receiving an ICI developed myocarditis [14-16]. Despite its rarity, ICI- related myocarditis can have serious clinical consequences and contribute to morbidity and mortality. In one recent review, Mir et al, found that 45 of 99 patients (45%) with ICI-associated cardiotoxicity had myocarditis; the overall fatality rate was 35% [17]. Furthermore, patients with myocarditis, complete heart block, conduction abnormalities, or ventricular arrhythmias had notably higher mortality rates than those with/without. Survival outcomes did not vary with the use of steroids. However, 9 of 12 patients treated with immunosuppressive agents (such as infliximab, mycophenolate, intravenous immunoglobulin, and anti-thymocyte globulin) and/or plasmapheresis survived. Our patient, who received only 1 dose of pembrolizumab, had no response to steroids or infliximab given in a timely manner, underscoring the complexity of managing cardiac irAEs.

According to the American Society of Clinical Oncology (ASCO) clinical practice guidelines for the management of irAEs in patients receiving ICIs, clinicians should have a high level of suspicion that new symptoms are treatment-related. ASCO recommends that, for grade 1 toxicities (with the exception of some neurologic, hematologic, and cardiac toxicities), ICIs should be continued with close monitoring. For most grade 2 toxicities, ICIs should be held, and treatment with corticosteroids (0.5-1 mg/kg/d) should be considered. For grade 3 toxicities, high-dose corticosteroids (prednisone 1-2 mg/kg/d or intravenous methylprednisolone 1-2 mg/kg/d) should be given for at least 4-6 weeks. If symptoms do not improve after 48-72 hours of high-dose corticosteroid, infliximab may be considered for some toxicities. Grade 4 toxicities warrant the permanent discontinuation of ICIs in most cases [18].

When our patient presented to the emergency department, we suspected that immune-mediated myocarditis was the cause of his signs and symptoms. For patients who present with signs or symptoms indicative of immune-mediated myocarditis, electrocardiography, echocardiography, and chest x-ray and laboratory tests for troponin and brain natriuretic peptide levels are recommended to assess for potential cardiovascular irAEs. A cardiology consult should be considered for further assessment. Patients found to have myocarditis should be managed with high-dose corticosteroids, and cardiac symptoms should be treated according to American College of Cardiology/American Heart Association guidelines. For patients who do not immediately respond to high-dose corticosteroids, cardiac transplant rejection-level doses of corticosteroids (1 g methylprednisolone per day), along with mycophenolate, infliximab, or anti- thymocyte globulin, should be considered [19]. Our patient was followed with this diagnostic algorithm and was treated with steroids, infliximab, and plasmapheresis.

Conclusion

As ICI, treatment becomes more commonplace, emergency medicine physicians will continue to play an important role in the care of this patients. Emergency medicine physicians will have to not only diagnose and treat patients presenting with irAEs in a timely manner but also initiate multidisciplinary team coordination. irAEs are

still being understood, and emergency medicine physicians are in the position to help develop protocols for the acute diagnosis and management of patients receiving ICIs.

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