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MINI-FOCUS ISSUE ON HEART FAILURE

BEGINNER

CASE REPORT: CLINICAL CASE

A Fatal Case of Pembrolizumab-Induced Myocarditis in Non–Small Cell Lung Cancer

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ABSTRACT

Immune channel inhibitor–induced myocarditis is rare, and its management is challenging. Recently, guidelines were established for all ICIs, yet they do not take into account individual drug toxicities or screening protocols for prevention. We present a rare case of rapidly progressive pembrolizumab-induced fatal myocarditis in an initially asymptomatic patient. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2020;2:426–30) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 77-year-old asymptomatic white male with stage IV non-small cell lung cancer (NSCLC), who had completed his second cycle of pembrolizumab, carboplatin, and pemetrexed 3 weeks earlier, was referred to the emergency department for observation from an outpatient cancer center due to new-onset right bundle branch block and premature ventricular contractions detected before port-a-cath placement. Review of systems was negative for chest pain, dyspnea, orthopnea, dizziness, or palpitations. Vital signs were stable. Physical examination was unremarkable. Stat electrocardiogram showed ST-segment elevation in V_3 to V_5 anteroseptal leads with new intraventricular block (**Figure 1**). No prior electrocardiograms were available for comparison.

LEARNING OBJECTIVES

- To review guidelines for the management of immune channel inhibitor–induced myocarditis.
- To establish the need for future studies involving pembrolizumab, its adverse effects, and screening tools to prevent fatal toxicities.

PAST MEDICAL HISTORY

The patient had a history of NSCLC, hypertension, deep vein thrombosis, cellulitis, and right eye melanoma resection.

DIFFERENTIAL DIAGNOSIS

In this asymptomatic patient, a wide differential diagnosis was considered, with myocardial infarction most concerning, followed by myocarditis/pericarditis, pulmonary embolism, and pneumonia.

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INVESTIGATIONS

Emergent troponin testing revealed a level of 37.81 ng/ml. Anticoagulation therapy and cardiac catheterization were initiated after an episode of hypotension and tachycardia and showed normal coronary arteries. Pulmonary embolism was subsequently ruled out with computed tomography-angiography of the chest. Serial troponin level tests (**Table 1**) were ordered. Transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging were scheduled.

MANAGEMENT

Development of mild fatigue on day 2 prompted an emergent TTE, showing normal structure and function with a left ventricular ejection fraction (LVEF) of 55% to 60% (**Figure 2**). Methylprednisolone 1,000 mg was initiated for suspected myocarditis. Carvedilol and atorvastatin were given. The patient developed stable sustained ventricular tachycardia (VT) with hypotension, and amiodarone was administered. Sinus rhythm was eventually restored.

Repeat TTE on day 3 after worsening hypotension and severe fatigue showed global dyskinesia and severely reduced LVEF of approximately 20% to 25% (**Figure 2**). Low-dose milrinone drip was started. Antithymocyte globulin (ATG) and intravenous immunoglobulin therapy (IVIG) were considered but, because of poor clinical status and lack of resources, were not given. An episode of sustained VT with hypotension to 50/30 mm Hg ensued; 200 J synchronized cardioversion successfully converted the patient into sinus rhythm. The family was notified, and the code status was changed to do not resuscitate/do not intubate. Subsequently, the patient developed pulseless VT and died.

DISCUSSION

Immune checkpoint inhibitors (ICIs) are a group of medications targeting binding sites on tumor cells: the PD-1 receptor, PD-L1, and CTLA-4. Binding of ICIs inhibits a downstream tumor-protective immunologic response, allowing for an appropriate attack on cancerous cells (**Figure 3**) (1,2).

Many studies regarding ICIs pertain to ipilimumab and nivolumab (anti-CTLA4 and anti-PD-1, respectively) in the treatment of melanoma. More recently, pembrolizumab was approved for treatment of NSCLC. Studies highlighting the benefits of these medications, either alone or in combination with chemotherapy, have also exposed the increased prevalence of ICI-induced adverse effects.

ABBREVIATIONS AND ACRONYMS

ATG = anti-thrombocyte globulin

ICI = immune channel inhibitor

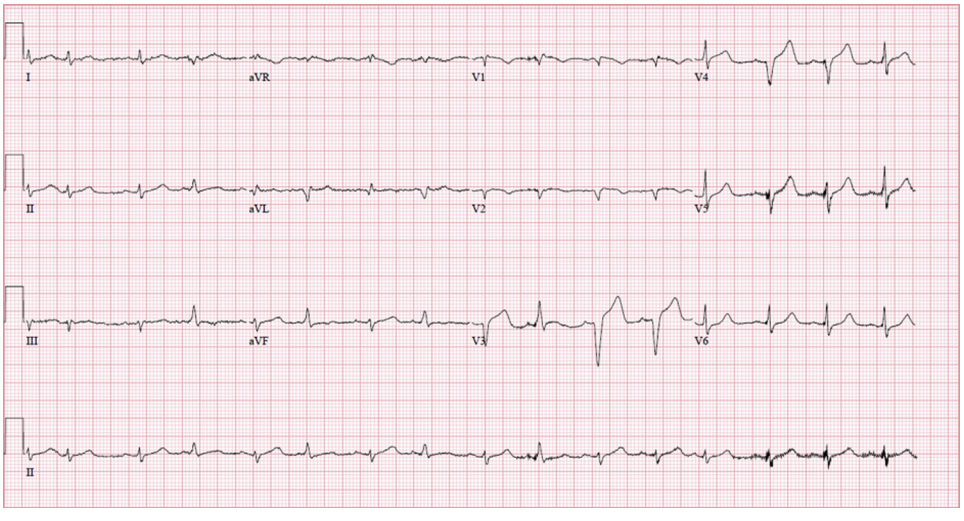
LVEF = left ventricular ejection fraction

NSCLC = non-small cell lung cancer

TTE = transthoracic echocardiogram

VT = ventricular tachycardia

FIGURE 1 Electrocardiogram on Admission



Evidence of low-voltage, questionable multiple premature atrial contractions with aberrant conduction versus premature ventricular contractions, intraventricular block, and ST-segment elevation in leads V_3 to V_5. This is suggestive of myocarditis, but ST-segment elevation myocardial infarction cannot be ruled out.

TABLE 1 Troponin Trend

Day of Therapy	Troponin Level, ng/ml
Day 1 (before steroid therapy)	37.81
	45.48
Day 2 (after starting steroid therapy)	44.63
Day 3	41.46
	45.44

Failure of troponin levels to decline following initiation of steroid therapy led to serious concern about further decompensation.

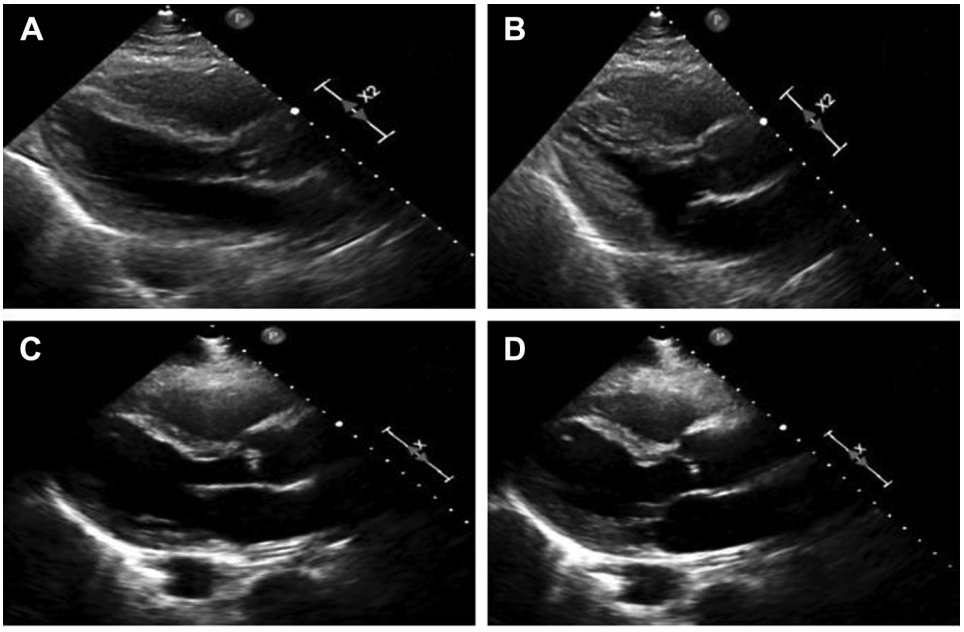
More recently, a review elucidated the adverse effects of ICIs as monotherapy and combination therapy (3,4).

The incidence of fatal ICI-associated adverse events is estimated to be between 0.3% and 1.3%. Fatalities with ICIs tend to occur early in the treatment course, irrespective of the ICI used but more often in combination therapy. The median time of onset for a fatal toxic event is approximately 14.5 days for ICI combinations, compared with 40 days in monotherapy. A meta-analysis of 333 patients showed colitis to be the most frequent cause of death with anti-CTLA-4 antibodies. Fatalities with anti-PD-1 or anti-PD-L1 antibodies were mainly due to pneumonitis, hepatitis, and neurotoxic effects. In patients receiving combination therapies, ICI-related deaths were mainly attributed to colitis or myocarditis. Of note, patients who develop myocarditis have the highest fatality rate (52 of 131 events reported), with 22 fatalities occurring after combination therapy, 3 with ipilimumab alone, and 27 in patients taking either a PD-1 or PD-L1 regimen (3,4).

The prevalence of myocarditis is 1.14%, with a median time to onset of 34 days. Recent studies using screening troponin levels to detect the development of myocarditis failed to show its utility (4,5). However, in either study, pembrolizumab (an anti-PD-1 receptor) was not under scrutiny. Further studies involving phenotype-specific tumor expression in NSCLC may subcategorize patients with increased risk of myocarditis and other major adverse cardiac events after pembrolizumab, as seen in studies with melanoma (6).

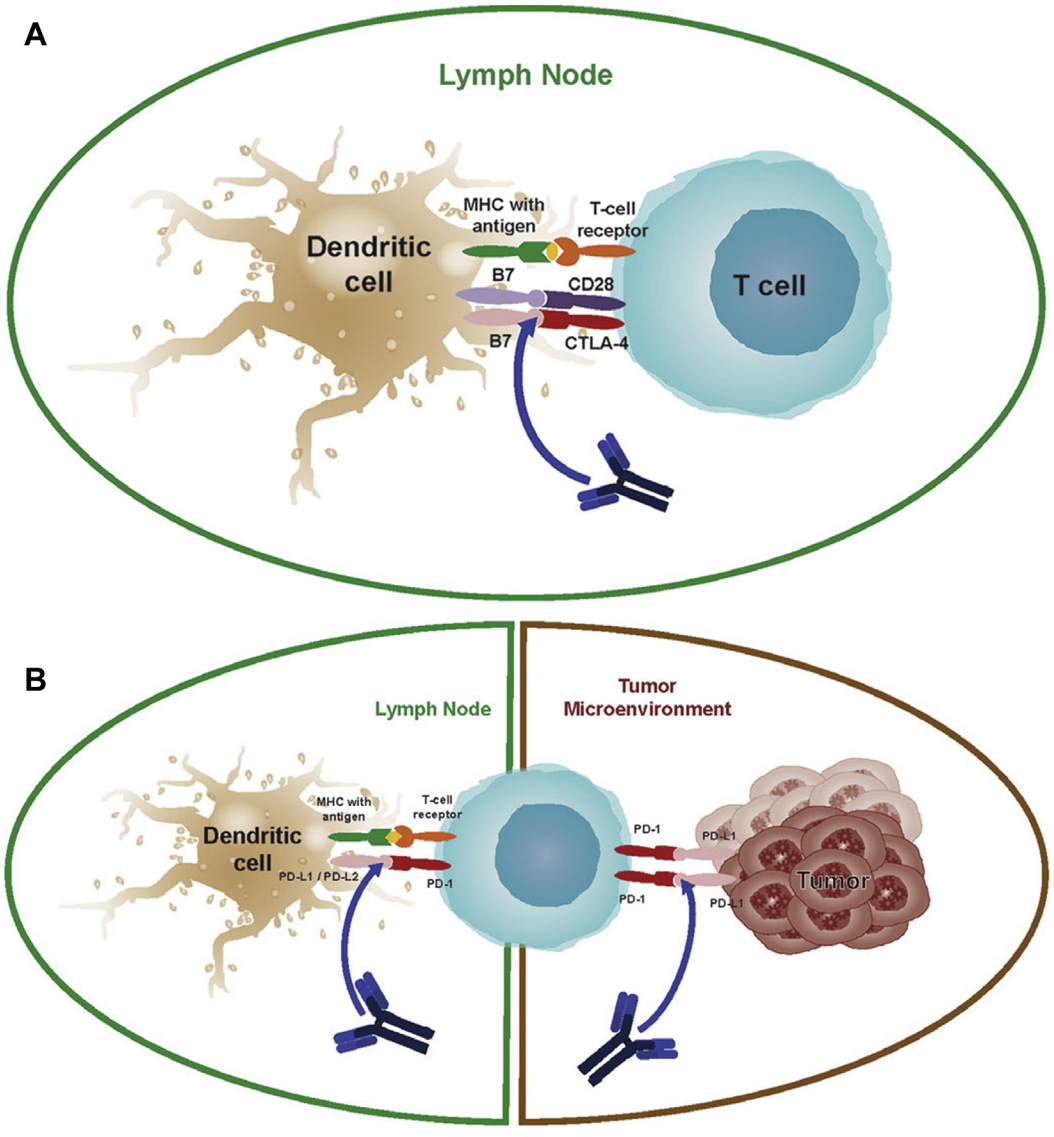
Cardiac magnetic resonance imaging is the criterion standard noninvasive test for myocarditis. The Lake Louise criteria are deemed consistent with myocarditis if 2 of the following 3 findings are

FIGURE 2 Parasternal Long-Axis View of the Heart



The **(A)** diastolic and **(B)** systolic function of the left ventricle on day 2 with a left ventricular ejection fraction of 55% to 60%.
The **(C)** diastolic and **(D)** systolic function of the left ventricle <24 h later, with depressed left ventricular ejection fraction at 20% to 25%.

FIGURE 3 Immunologic Response to Antigens

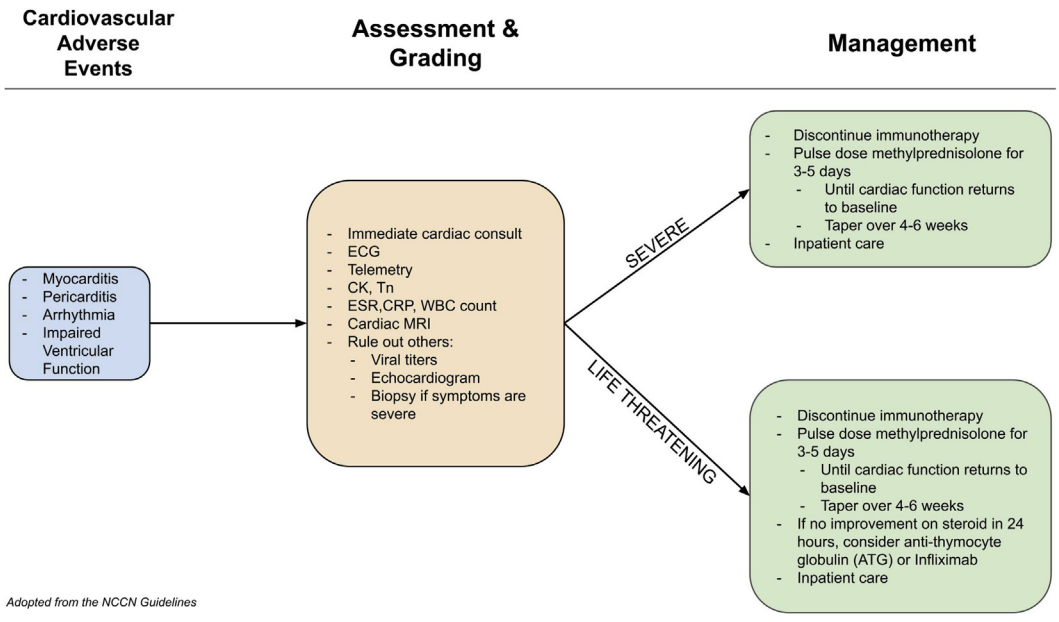


(A) The normal immunologic response to antigens in lymph nodes. **(B)** Binding of tumor PD-L1 to bind PD-1 receptors on T cells. Shown is a monoclonal antibody directed toward PD-1 receptors. Reprinted with permission from Sheng et al. (2).

present: evidence of myocardial edema, hyperemia and capillary leakage, and/or late gadolinium enhancement in at least 1 focal lesion with non-ischemic distribution. The criterion standard invasive test for diagnosis is an endomyocardial biopsy that shows a T-cell-predominant lymphocytic infiltrate atypical for an ischemic event (7).

The American Society of Clinical Oncology recommends stopping the ICI, monitoring in the coronary care unit, and administering prednisone 1 to 2 mg/kg/day. Failure to respond warrants methylprednisolone 1 g/day in combination with either mycophenolate mofetil, infliximab, or anti-ATG. Alternatively, the National Comprehensive Cancer Network suggests initial therapy of methylprednisolone with earlier use of ATG or intravenous immunoglobulin (**Figure 4**). In the presence of moderate to severe heart failure, infliximab has been found to worsen heart failure and is contraindicated in high doses (8–10).

FIGURE 4 National Comprehensive Cancer Network Guidelines for the Management of Immune Channel Inhibitor-Induced Cardiovascular Adverse Events



The use of methylprednisolone is the initial treatment of choice.

FOLLOW-UP

After our patient's death, a request for autopsy and biopsy of the heart to confirm the diagnosis of ICI-induced myocarditis was respectfully denied by the family.

CONCLUSIONS

Pembrolizumab, an anti-PD-1 checkpoint inhibitor, has proven efficacious in the treatment of many cancers, most notably melanoma and NSCLC. Although rare, rapid progression of fatal myocarditis, as in our patient, is serious and warrants a better understanding of its etiology, screening, and management to reduce adverse outcomes.

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KEY WORDS fatal, myocarditis, pembrolizumab