Acute Lymphocytic Myocarditis With Anti-PD-1 Antibody Nivolumab

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In late December 2015, a 69-year-old woman presented with general malaise and palpitation lasting a few days. She had choroidal malignant melanoma with liver and bone metastases and had undergone 3 cycles of anticancer treatment with an anti-PD-1 (programmed cell death protein 1) antibody nivolumab (2 mg/kg of body weight every 3 weeks) from October 2015 to early December 2015. Two weeks had elapsed since the last treatment with nivolumab. On physical examination, blood pressure was 121/83 mm Hg and heart rate 110 beats per minute. ECG showed ST-segment elevation in leads II, III, and aVF. A bedside rapid assay for cardiac troponin T was positive, and the concentrations of creatine kinase and creatine kinase MB-isozyme were increased to be 728 IU/L and 48.7 U/L, respectively. Echocardiography showed diffuse hypokinesis of the left ventricle (ejection fraction 30.2%). Emergency coronary angiography revealed normal epicardial coronary arteries, and acute myocarditis was suspected as a cause of left ventricular dysfunction. Despite continuous dobutamine infusion, low output symptoms remained unchanged and pulmonary congestion was worsened. On day 5, right heart catheterization was performed, showing an elevated right atrial pressure (17 mm Hg) and a decreased cardiac index (1.92 L/min/m²). Myocardial biopsy was also done for histological analysis. From day 5, oral prednisolone was initiated at the dose of 2 mg/kg of body weight per day (100 mg/d), and her symptoms were gradually improved. The dose of prednisolone was tapered at 5 mg per week without recurrence of heart failure. Left ventricular ejection fraction was increased to 55% on follow-up echocardiography. On day 78, she was discharged on prednisolone 15 mg/d. Myocardial biopsy sample that had been taken on day 5 demonstrated lymphocytic infiltration, with a predominance of CD8-positive, PD-1-negative T-cells (Figure 1). Serological analysis of paired serum samples for cardiotropic viruses was negative. Analysis of nucleic acid extracted from myocardial tissue by multivirus real-time polymerase chain reaction was also negative. When last seen 5 months later, she was asymptomatic without heart failure or recurrent tumor growth. Extent of both choroidal and liver metastatic lesions was markedly improved (Figure 2).

Human monoclonal anti-PD-1 antibody nivolumab belongs to a new class of anticancer agents known as immune checkpoint inhibitors and revitalizes inhibitory T-lymphocytes by blocking ligand binding to PD-1. Nivolumab is being widely used for malignant melanoma, nonsmall cell lung cancer, and renal cell carcinoma. To the best of our knowledge, our patient is the first reported case of biopsy-proven, acute lymphocytic myocarditis that occurred after the administration of nivolumab. Although symptomatic heart failure has been only rarely recognized in large-scale clinical trials of nivolumab, clinically silent lymphocytic myocarditis was reported in an autopsy study of a patient with melanoma treated with ipilimumab and nivolumab. Autoimmune myocarditis during the treatment with another PD-1 inhibitor pembrolizumab was recently reported in a 73-year-old woman with metastatic uveal melanoma.

The mechanism whereby anti–PD-1 antibody causes myocarditis is not well understood, but several lines of experimental evidence suggest that PD-1 is protective against autoimmune-related organ damage. For example, PD-1 deficiency was associated with inflammatory myocyte death in T-cell-mediated myocarditis. Intriguingly, PD-1-deficient mice developed a heart failure mimicking dilated cardiomyopathy. Use of nivolumab in patients where other treatments have failed is likely to expand in the future, but it is currently unknown which patient is predisposed to cardiac complication. Regular echocardiographic examination of left ventricular function may, therefore, be of clinical importance, and early initiation of prednisolone should be considered in patients complicated by progressive heart failure during immune checkpoint inhibitor therapy.

Disclosures

None.

References

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Key Words: adverse events  ■  heart failure  ■  immune checkpoint inhibitor  ■  melanoma  ■  myocarditis

Figure 1. Hematoxylin-eosin staining of myocardial tissue showing lymphocytes infiltration (A) with a predominance of CD4-negative (B), CD8-positive (C), and PD-1-negative cells (D). A black bar indicates 50 μm.
Figure 2. Computed tomographic scans of the liver before nivolumab treatment (A) and at 5 months after discharge (B).
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Circ Heart Fail. 2016;9:
doi: 10.1161/CIRCHEARTFAILURE.116.003514
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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