

Immune Checkpoint Inhibitor-Related Cardiotoxicity

Barry Trachtenberg, M.D.^a; Fahd Hussain, M.D.^b; Akash Mukherjee, M.D.^a; Raquel Araujo-Gutierrez, M.D.^a; Sai ravi kiran Pingali, M.D.^a

^aHOUSTON METHODIST HOSPITAL, HOUSTON, TEXAS; ^bHOUSTON METHODIST RESEARCH INSTITUTE, HOUSTON METHODIST HOSPITAL, HOUSTON, TEXAS

INTRODUCTION

Immune checkpoint inhibitors have shown durable and promising activity against several cancers, thereby establishing their role in the evolving treatment landscape. However, their increased use in oncology patients is revealing a growing number of immune-related cardiovascular events, which is contrary to the reported lower incidence in previous clinical trials.¹⁻⁶ We report two cases of cardiotoxicity related to the use of immune checkpoint inhibitors to further highlight this potentially fatal adverse event and the associated diagnostic challenges.

CASE 1

A 79-year-old Caucasian man with a history of stage IV mantle cell lymphoma with bone marrow involvement presented to the emergency department (ED) with complaints of dyspnea and fever for 1 day. He had experienced frequent remissions and relapses since his diagnosis in 2006, and subsequent treatments with chemotherapy, radiotherapy, and autologous bone marrow transplant had rendered him tremendously immunosuppressed. He remained on monthly intravenous immunoglobulin (IVIG) infusions for recurrent sinopulmonary infections and had been treated for several years for aggressive squamous carcinomas of the scalp. Ten weeks before presentation, he was diagnosed with treatment-related acute myeloid leukemia (AML) and was started on palliative chemotherapy with decitabine and nivolumab, which is an anti-programmed-death-1 receptor antibody. He came to the ED a week after receiving his third dose of nivolumab. The physical exam was unremarkable except for high fever (102.8° F) and tachycardia. Pertinent labs revealed neutropenia, elevated brain natriuretic peptide (3221 pg/mL), lactate dehydrogenase (362 U/L), troponins (0.50 ng/mL), and negative blood and urine cultures. A viral respiratory panel was performed in addition to cytomegalovirus and Epstein-Barr virus serology, and all were negative. An electrocardiogram showed sinus tachycardia with occasional premature ventricular contractions (PVCs). On transthoracic echo, the left ventricle (LV) size was mildly enlarged (5.8 cm) and ejection fraction (EF) was estimated to between 25% and 29%. His right ventricle (RV) was also enlarged, with moderately to severely depressed function, and he had impaired renal and hepatic function. An echocardiogram performed several months before initiation of nivolumab was normal. Endomyocardial biopsy (EMB) was not attempted due

to severe thrombocytopenia, and cardiac magnetic resonance imaging (MRI) with gadolinium and coronary angiography were contraindicated due to acute renal insufficiency.

All chemotherapy was suspended, and the patient was started on diuretics and inotropic support. There was clinical suspicion for myocarditis secondary to nivolumab, and steroids were administered empirically. One month later, after renal recovery occurred, he underwent a cardiac MRI that showed moderately depressed EF and absence of delayed gadolinium enhancement. After a prolonged hospital course, he was transferred to inpatient rehabilitation for continued care. Unfortunately, the patient died 3 months after his presentation due to complications from heart failure and AML.

CASE 2

A 77-year-old male was referred to the cardio-oncology clinic for heart failure with reduced and worsening EF (20-25%). He had a history of hypertension, type 2 diabetes mellitus, chronic kidney disease (CKD), and stage 3 non-small-cell lung cancer (NSCLC). Before the onset of cancer, he had a mildly depressed LVEF (45-50%) of unknown etiology. His NSCLC was initially treated with cisplatin-based chemotherapy but was switched to nivolumab 6 months prior to referral. He complained of several weeks of orthopnea and dyspnea on exertion, requiring him to be on home oxygen. On physical examination, the patient was dyspneic and had ectopy, jugular venous distention, and peripheral edema. An electrocardiogram showed atrial fibrillation with PVCs. Given his risk factors for coronary artery disease, a coronary angiogram was recommended but was refused by the patient due to his history of CKD and fear of nephrotoxicity. Cardiac MRI with adenosine was ordered, and findings were indicative of non-ischemic cardiomyopathy with absence of ischemic changes and 2% mid-myocardial scar burden. The patient declined an EMB to evaluate for checkpoint inhibitor (CPI) myocarditis. His nivolumab was held due to a temporal drop in EF with its initiation, and he was initiated on goal-directed medical therapy for his heart failure. After several months, his EF improved back to his pretreatment baseline of between 45% and 50%.

DISCUSSION

The use of immune CPI therapy in the management of malignancies such as melanoma and NSCLC has advanced the

field of oncology with its improved clinical outcomes. However, its potential to activate the immune system may cause rare but potentially fatal adverse effects. A recent report of fatal and fulminant myocarditis was described in two patients on dual CPI therapies.¹ According to subsequent retrospective analysis of a pharmaceutical database, there is a 0.27% incidence of myocarditis with the combination of two CPIs (i.e., ipilimumab, a CTLA-4 inhibitor, and nivolumab), whereas there is only a 0.06% risk of developing fulminant myocarditis with monotherapy.¹ However, more recent reports suggest that development of myocarditis on monotherapy may be more common.⁶ For example, in April of this year, a multisite registry reported 35 cases of CPI-associated myocarditis, with an estimated incidence of 1.1%.⁸ Most patients who were part of immunotherapy trials did not have cardiac monitoring while receiving CPI therapy, so the true incidence of the disease is not known.

The diagnosis of myocarditis in general is challenging due to a notoriously poor gold standard: the Dallas criteria. These criteria require an invasive EMB that is infrequently performed, is poorly sensitive, and has poor interobserver reliability.⁷ A patient with myocarditis can present with very nonspecific symptoms such as fatigue and nausea, both of which are common side effects of any chemotherapy. The cases of CPI-induced myocarditis that have been reported in the literature suggest that early detection through cardiac evaluation may help the physician diagnose this potentially fatal disease. However, in one retrospective analysis, cardiac MR (CMR) showed late gadolinium enhancement (LGE) in only 23% of patients ($n = 13$) and myocardial edema in only 33% ($n = 15$), which indicates that CMR itself was not very sensitive for the diagnosis of CPI myocarditis.⁶ In contrast, EMB was very sensitive and much higher for CPI myocarditis than for lymphocytic myocarditis, although this conclusion is limited by a small sample size. Another multisite registry recently reported that 26% of patients diagnosed with myocarditis had absent delayed gadolinium enhancement.⁸

The two largest reports thus far have indicated that cardiotoxicity occurs fairly early after the initiation of CPI, with medians of 34 and 65 days, respectively.^{6,8} Differences from these reports are presented in Table 1. Left ventricular systolic dysfunction occurred in 49% to 79% of patients with CPI myocarditis. Troponin elevation varied greatly, with one study showing elevation in 46% of myocarditis patients and another showing elevation in 94% of patients. Other cardiovascular events included atrial fibrillation (30%), ventricular arrhythmia (27%), and conduction disorders (17%).⁶ In addition, 67% of patients on corticosteroid therapy showed complete reversibility of LV systolic function. Death due to cardiovascular causes occurred in 17% to 27% of

patients. Risks associated with death included conduction abnormalities and the use of ipilimumab-nivolumab combination therapy.⁶

One possible explanation for development of CPI myocarditis could be the role of PD-1 receptors in myocardium that suppress T-cell-mediated autoimmune myocarditis and potential blunting of this cardioprotective mechanism by PD-1 or PD-L1 inhibitor use. Nishimura et al. showed that disruption of the gene encoding negative immunoregulatory receptor PD-1 in mice caused dilated cardiomyopathy with severely impaired contraction leading to sudden death by congestive heart failure. All the affected mice with PD-1-receptor-deficient expression showed diffuse deposition of IgG on the surface of cardiomyocytes as well as high titer of circulating IgG autoantibodies against myocardial protein.⁹ Similarly, post-mortem analysis of both patients by Johnson et al. showed infiltration of CD3+, CD8+ T-cells in the myocardium and cardiac conduction system, indicative of potential autoimmune myocarditis. Another interesting finding was the increased expression of PD-L1 in the injured myocardium, probably to mitigate T-cell-mediated injury in an autoimmune inflammatory setting.¹ Possible blunting of this cardioprotective mechanism by CPI could potentially explain the observed cardiotoxicity in such patients.

Prior studies did highlight the importance of establishing a prompt diagnosis of myocarditis in the setting of CPI due to its association with higher mortality and potential improvement by steroid therapy. However, diagnosing this time-sensitive complication can be challenging. Both cases described above were primarily diagnosed on the basis of clinical suspicion and have not definitively proved to be cases of CPI myocarditis; in fact, we report these cases because they exemplify and highlight the immense challenges in diagnosing this condition. In case 2, the patient's LVEF dropped several months after he started on CPI therapy and improved several weeks after it was stopped (and medical therapy for heart failure initiated). Although cases of fulminant myocarditis have been reported, there may be cases that involve a more indolent course, or "smoldering" myocarditis.

As challenging as it is to diagnosis myocarditis in general, it can be an even greater challenge in cancer patients treated with CPI who may have comorbidities and adverse events that preclude certain diagnostic tests. Therefore, the ability to diagnose myocarditis requires a high index of clinical suspicion along with troponin and electrocardiographic testing and consideration of EMB and cardiac MRI. With the current surge in CPI immunotherapy use, it will be crucial to devise a specific protocol for monitoring patients on checkpoint inhibitors and to define the true incidence and range of clinical manifestations.

CLINICAL CHARACTERISTICS	ESCUDIER ET AL. ⁶ N = 30	MAHMOOD ET AL. ⁸ N = 35
Time from CPIs to onset of myocarditis, median (range), days	65 (2-454)	34 (21-75)
CPI infusions prior to onset, median (range), n	3 (1-33)	3 ± 3*; 5.2 ± 8
Left ventricular systolic dysfunction (LVSD)	79%	49%
Abnormal EKG	NR	89%
Atrial fibrillation	30%	NR
Ventricular arrhythmia	27%	NR
Conduction abnormalities	17%	NR
Pericardial effusion	7%	17%
MRI		
Late gadolinium enhancement	23%	74%
BNP or NT pro-BNP elevation	100%	66%
Troponin elevation	46% [†]	94% [‡]
Lymphocyte infiltration (histology)	89%	100%
Corticosteroids	70%	89%
Complete LVSD reversibility	67%	NR
Death from cardiovascular causes	27%	17%

* Values are represented as mean ± standard deviation and refer to groups subcategorized by presence or absence of MACE, respectively.

Table 1.

Clinical characteristics of checkpoint inhibitor myocarditis.^{6,8} CPI: checkpoint inhibitor; EKG: electrocardiogram; MRI: magnetic resonance imaging; NT pro-BNP: N-terminal pro brain natriuretic peptide; NR: not reported; †: troponin I; ‡: troponin T

Conflict of Interest Disclosure:

The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Keywords:

checkpoint inhibitor, myocarditis, immunotherapy, cardiotoxicity

REFERENCES

1. Johnson DB, Balko JM, Compton ML, et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. *N Engl J Med*. 2016 Nov 3;375(18):1749-55.

2. Behling J, Kaes J, Munzel T, Grabbe S, Loquai C. New-onset third-degree atrioventricular block because of autoimmune-induced myositis under treatment with anti-programmed cell death-1 (nivolumab) for metastatic melanoma. *Melanoma Res.* 2017 Apr;27(2):155-8.
3. Semper H, Muehlberg F, Schulz-Menger J, Allewelt M, Grohe C. Drug-induced myocarditis after nivolumab treatment in a patient with PDL1- negative squamous cell carcinoma of the lung. *Lung Cancer.* 2016 Sep;99:117-9.
4. Wang DY, Okoye GD, Neilan TG, Johnson DB, Moslehi JJ. Cardiovascular Toxicities Associated with Cancer Immunotherapies. *Curr Cardiol Rep.* 2017 Mar;19(3):21.
5. Varricchi G, Galdiero MR, Tocchetti CG. Cardiac Toxicity of Immune Checkpoint Inhibitors: Cardio-Oncology Meets Immunology. *Circulation.* 2017 Nov 21;136(21):1989-92.
6. Escudier M, Cautela J, Malissen N, et al. Clinical Features, Management, and Outcomes of Immune Checkpoint Inhibitor-Related Cardiotoxicity. *Circulation.* 2017 Nov 21;136(21):2085-7.
7. Trachtenberg BH, Hare JM. Inflammatory Cardiomyopathic Syndromes. *Circ Res.* 2017;121(7):803-18.
8. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. *J Am Coll Cardiol.* 2018 Apr 24;71(16):1755-64.
9. Nishimura H, Okazaki T, Tanaka Y, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. *Science.* 2001 Jan 12;291(5502):319-22.