BRIEF REPORT

# Immune Checkpoint Inhibitor–Associated Pericarditis

Mehmet Altan, MD,[a,b,*] Maria I. Toki, MD,[c] Scott N. Gettinger, MD,[a] Daniel E. Carvajal-Hausdorf, MD,[c,d] Jon Zugazagoitia, MD,[c] John H. Sinard, MD, PhD,[c] Roy S. Herbst, MD, PhD,[a] David L. Rimm, MD, PhD[a,c]

[a]*Section of Medical Oncology, Yale School of Medicine, New Haven, Connecticut*
[b]*Department of Thoracic/Head & Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas*
[c]*Department of Pathology, Yale School of Medicine, New Haven, Connecticut*
[d]*Anatomic Pathology, Clinica Alemana-Facultad de Medicina Universidad de Desarrollo, Vitacura, Santiago, Chile*

Received 27 November 2018; revised 20 February 2019; accepted 28 February 2019
Available online - 6 February 2019

**ABSTRACT**

Side effects of immune checkpoint inhibitors, termed immune-related adverse events, are relatively common, but immune checkpoint inhibitor–mediated cardiotoxicities are rare; however, they can be serious and potentially fatal. Pericarditis is an infrequent cardiac toxicity of immunotherapy and predisposing factors remain unknown. Here we report three patients with NSCLC who developed pericarditis during therapy with programmed death 1/programmed death ligand 1+/- CTLA-4 inhibitors. We review the clinical presentation of these three cases and histopathologic findings from autopsies from the first two patients and a pericardial sampling that has been obtained from a pericardial window procedure in the third patient who recovered from the pericarditis episode. We also discuss the potential mechanisms, as well as what is known about pericarditis secondary to immune-related adverse events.



*Keywords:* Immune-related adverse events; Pericarditis; NSCLC

## Introduction

Despite remarkable progress made in the treatment of several advanced cancers since the introduction of immune checkpoint inhibitors (ICIs), immune-related adverse events (irAEs) associated with unrestrained modulation of the immune system remain a challenge.

Cardiotoxicity is a potentially fatal complication associated with immunotherapy. Myocarditis with clinical presentations ranging from asymptomatic cardiac biomarker elevation to heart failure, arrhythmia, cardiac fibrosis, cardiogenic shock, and pericarditis have been reported in clinical trials and as post-marketing experience with immunotherapy.[1-6] Pericarditis is an infrequent cardiac toxicity of immunotherapy, and predisposing factors remain unknown. Thus far in the literature, few cases have been described with pericardial effusion and/or pericarditis.[7]

*Corresponding author.

Drs. Altan and Toki contributed equally to this article.

*Disclosure: Dr. Altan has received grants from Bristol-Myers Squibb and Eli Lilly. Dr. Gettinger has received grants from Bristol-Myers Squibb, Nektar Therapeutics, Iovance Biotherapeutics, Genentech, and Takeda/ARIAD; and has received personal fees from Bristol-Myers Squibb and Nektar Therapeutics. Dr Herbst has received honoraria from for following: Consulting: Abbvie Pharmaceuticals, ARMO Biosciences, AstraZeneca, Biodesix, Bristol-Myers Squibb, Eli Lilly and Company, EMD Serrano, Genentech/Roche, Genmab, Heat Biologics, Loxo Oncology, Merck and Company, Nektar, NextCure, Novartis, Pfizer, Sanofi, Seattle Genetics, Shire PLC, Spectrum Pharmaceuticals, Symphogen, Tesaro, Tocagen. Advisory Boards: Neon Therapeutics, Infinity Pharmaceuticals, NextCure. Research support: AstraZeneca, Eli Lilly and Company, Merck and Company. He is a member of the board of directors (non-executive/independent) for Junshi Pharmaceuticals. Dr. Rimm has received grants from Astra Zeneca, Navigate/Novartis, Cepheid, Perkin Elmer, Ultivue, and Gilead Sciences; and has received personal fees from Bristol-Myers Squibb, Astra Zeneca, Merck, Navigate/Novartis, Agendia, Agilent, Bethyl Labs, Biocept, Cell Signaling Technology, Cepheid, OptraScan, Perkin Elmer, and Ultivue. The remaining authors declare no conflict of interest.*

Address for correspondence: Mehmet Altan, MD, Department of Thoracic/Head & Neck Medical Oncology, University of Texas MD Anderson Cancer Center, 1400 Holcombe Blvd, FC9.3058, Houston, Texas, 77030. E-mail: maltan@mdanderson.org



ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2019.02.026

In this brief report we describe three patients with NSCLC who developed pericarditis during therapy with programmed death 1 (PD-1)/programmed death ligand 1 (PD-L1) +/- cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitors. Tissue and associated clinicopathologic information was used after approval from the Yale Human Investigation Committee (protocol #9505008219).

## Case Presentation

### *Case 1*

A 72-year-old man with hypertension, coronary artery disease, and metastatic *KRAS*-mutant lung adenocarcinoma presented to the hospital with cardiac tamponade and in cardiac arrest. His lung cancer had been diagnosed 1 year previously and he progressed on standard chemotherapy. He received radiation to the right hilar mass (Fig. 1*A*) and was enrolled in a clinical trial with an anti–PD-L1 monoclonal antibody associated with a marked clinical and radiological response (Figs. 1*B* and *C*). His death was 78 days after starting therapy in a clinical trial with an anti–PD-L1 therapy. Autopsy revealed widespread tumor necrosis in all primary and metastatic sites with the exception of residual viable tumor in the left adrenal gland. The epicardial surface was covered by a hemorrhagic fibrinous exudate (Fig. 2).

### *Case 2*

A 65-year-old woman with type 2 diabetes mellitus, hypertension, and metastatic recurrent lung adenocarcinoma presented to a local hospital, with loss of consciousness and hypotension while she was being treated with anti–CTLA-4 and anti–PD-1 therapy as part of a clinical trial. Workup revealed cardiac tamponade. The patient was intubated and underwent a pericardial window procedure with drainage of 1 L of blood fluid

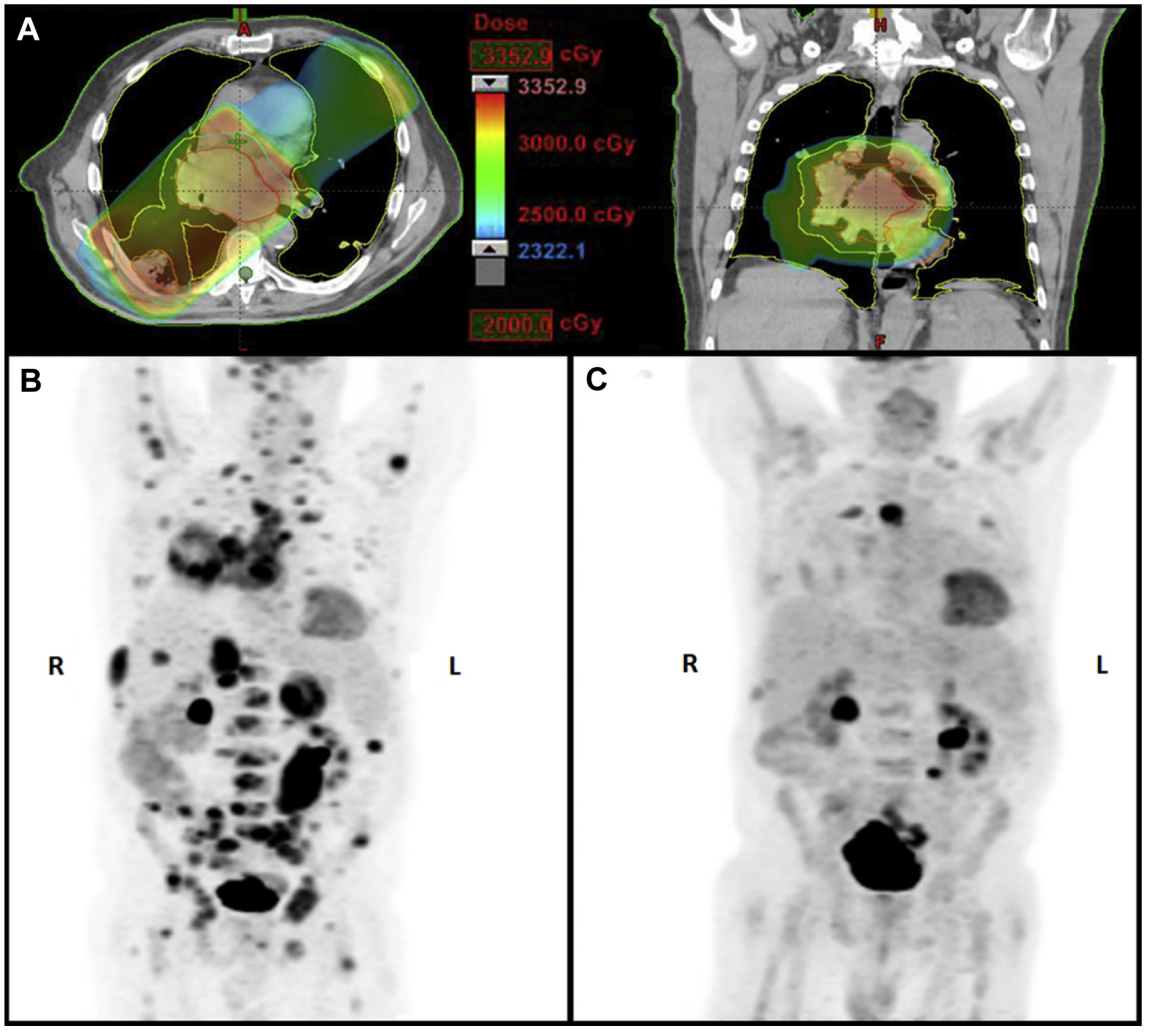


**Figure 1.** (*A*) Radiation fields for palliative right hilum radiation. (*B* and *C*) Imaging studies by positron emission tomography (*B*) pretreatment and (*C*) after four cycles of therapy, with marked clinical response, for case 1.

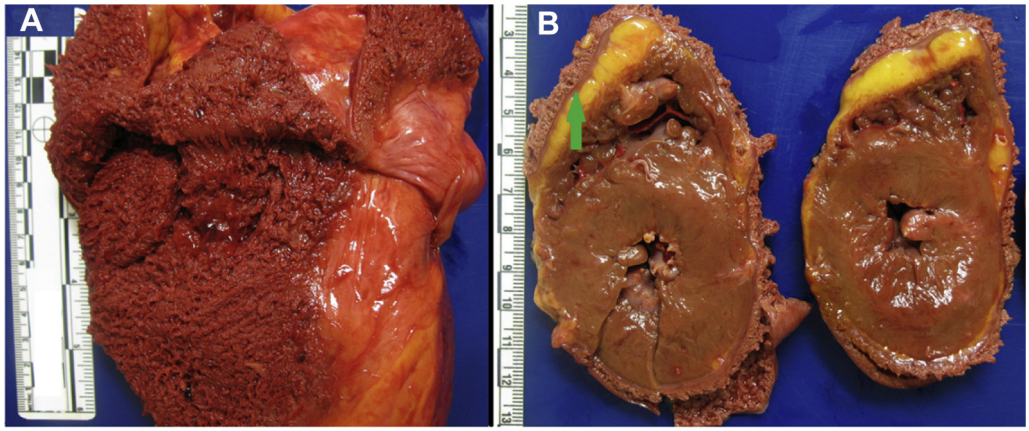


**Figure 2.** (*A*) Fibrinous pericarditis adherent to the parietal (reflected superiorly) and visceral pericardium. (*B*) Bread-loaf sections of the formalin-fixed heart showing a fibrinous, hemorrhagic exudate covering the heart and epicardial fat (*green arrow*). The epicardial surface is covered by a fibrinous exudate measuring 4- to 5-mm in thickness, representing a classic "bread and butter" pericarditis.

from the pericardial space which did not reveal malignant cells. There were elevated cardiac enzymes and decreased left ventricular function. A pacemaker was placed due to cardiac arrhythmias. Post-procedure, she had limited improvement in her metal status, and a brain magnetic resonance image showed multiple subacute infarcts without hemorrhage. She had no significant neurologic recovery and was transferred to inpatient hospice 13 days after the pericardial window procedure. She died 5 days later. Pre-existing hypertension was her only comorbid condition.

### *Case 3*

A 57-year-old man with metastatic lung adenocarcinoma presented with dyspnea, orthopnea, and bilateral lower extremity edema while on therapy with anti–PD-L1 therapy. Ninety-eight days after the first dose of immunotherapy, he was found to have cardiac tamponade and underwent a pericardial window procedure with full recovery. Post-procedure he was rechallenged with the same immunotherapy. Although he had no dose-limiting toxicities, he experienced progressive disease and discontinued therapy 3 months after his clinical presentation with pericarditis (Tables 1[8] and 2; further details of the clinical presentation including laboratory results and imaging studies are available in Supplementary Tables S1–S3).

## Histopathology Findings

### *Case 1*

Autopsy examination of the heart revealed that the parietal pericardium was up to 0.4-cm thick with the serosal surface being covered by a shaggy, fibrinous, hemorrhagic exudate. There was also a shaggy, fibrinous, hemorrhagic exudate surfacing the pericardium adherent to the epicardium (Figs. 2*A* and *B*). Microscopically, there was diffuse fibrinous pericarditis with a thick layer of fibrinous tissue adherent to the epicardium of the left and right ventricles, and an inflammatory infiltrate underlying the fibrinous tissue consisting of numerous lymphocytes, some macrophages, and occasional plasma cells. Additionally, there were small collections of lymphocytes, predominantly perivascular, identified within the myocardium of the left and right ventricles. No tumor cells were identified on the pericardial or epicardial surfaces. Immunohistochemical staining of the samples revealed the inflammatory infiltrate beneath the thick fibrinous layer on the epicardium to consist of numerous CD4+ and CD8+ T cells in a 1:1 ratio, some CD68+ macrophages, and scattered CD20+ B cells (Supplementary Figs. S1–S3). There were residual viable tumor cells in left adrenal gland, but no viable tumor cells noted in the right hilar and right lower lobe (Supplementary Figs. S4–S6).

### *Case 2*

At autopsy, the pericardium was markedly fibrotic and adherent to the anterior chest wall. There was a fibrinous pericarditis, with a mild chronic lymphocytic infiltrate and fibrin deposition. There was no evidence of acute inflammation in the pericardium, and no tumor cells were identified on the pericardial or epicardial surfaces (Supplementary Figs. S7–S9).

### *Case 3*

Histopathologic examination of the tissue from the pericardial window procedure revealed fragments of pericardium with fibrosis, hemorrhage, edema, moderate lymphoplasmacytic infiltrate, and fibrinous exudate with

Table 1. Clinical Characteristics of Three Patients

| Case No. | Age, Years | Sex | Histology | Smoking Status | Molecular Profile | Comorbid Problems | TNM Stage[a] | Pre-existing Cardiac Risk Factors | Clinical Symptoms at Presentation | Sites of Disease |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 73 | M | Adenocarcinoma | Former smoker (20 pack /year) | *KRAS* G12C mutant | Hashimoto's thyroiditis<br>Hypertension<br>—Coronary artery disease (with coronary artery stents)<br>Chronic Obstructive Pulmonary Disease | T4N2M1c | Coronary artery disease<br>Hypertension | Dyspnea, Hypotension<br>Hypoxia | Bilateral lungs, liver, spleen, pancreas, adrenal, peritoneum, and osseous metastasis |
| 2 | 65 | F | Adenocarcinoma | Former smoker (30 pack /year) | No driver mutation detected | Type 2 diabetes mellitus<br>Hypertension | T4N3M1c | Hypertension | Loss of consciousness<br>Hypotension | Bilateral lungs, bone, and periportal and peripancreatic lymph nodes |
| 3 | 57 | M | Adenocarcinoma | Former smoker (20 pack /year) | No driver mutation detected | No relevant past medical history | T3N1M1c | None | Dyspnea, Orthopnea, Bilateral lower extremity edema | Bilateral lung nodules, abdominal lung nodules, liver, and osseous metastasis |

[a]According to the American Joint Committee on Cancer Cancer Staging Manual Eighth Edition.
M, male; F, female.

organization, along with moderate macrophage infiltrate and focal neutrophilic infiltrate. No epicardium was observed (Supplementary Figs. S10–S12).

## Translation Studies

In quantitative immunofluorescence analysis, the expression of the immune cell markers (methods for multiplexed tumor infiltrating lymphocytes [TILs], TILs activation, and PD-L1/CD68 immunofluorescence staining and statistical analysis are in the Supplementary material) was assessed in 10 field-of-view hotspots for each sample (Fig. 3). TIL marker expression (CD4, CD8, and CD20) did not differ between primary tumor and toxicity site (Supplementary Fig. S13). Assessment of the macrophage population across sites revealed a uniformly higher CD68+ expression in the pericarditis samples, compared with baseline tumor biopsy samples which were obtained before immunotherapy ($p < 0.0001$). Notably, the CD68 protein expression was also high in available primary tumor samples at the time of toxicity compared with baseline samples. The expression of PD-L1 in the CD68+ cells was also statistically higher in the pericarditis samples compared with baseline tumor ($p < 0.0001$), with the primary tumor site having the highest PD-L1 expression in macrophages at the time of toxicity (Supplementary Fig. S14). In our study, pericardial tissue samples and pericardial fluid cytology did not reveal malignant cells and there was no positive PD-L1 expression outside the infiltrating immune cells in the pericarditis samples.

## Discussion

In contrast to the well-characterized temporal patterns of classic chemotherapy toxicities, the onset and duration of irAEs are unpredictable and predisposing factors for individuals to develop irAEs remain unclear.[9] Nearly all organs can be affected by immune-related toxicities. The case series presented here reports histologically confirmed pericarditis which developed during PD-1/PD-L1 ± CTLA-4 directed therapies.

Clinical presentation of pericarditis as an irAE can be insidious and asymptomatic, and the time to clinical presentation can be variable. In the literature, cardiac ICI-related cardiac toxicities have been reported to develop at a median of 65 days (range, 2 days to 454 days).[4] With its rare and nonspecific presentation, diagnosis can be delayed or missed, which can cause considerable difficulty in obtaining accurate data on incidence and prevalence. For the development of cardiotoxicity secondary to ICIs, multiple hypotheses are generated from clinical observation and preclinical work. These include off-target cross-reactivity of affinity-enhanced T cells, targeting an antigen shared by a tumor

**Table 2.** Treatment History and Response Data for Three Patients

| Case No. | Prior Therapies | Prior RT | Type of ICI | Time Elapsed Between Last Dose of Thoracic RT and Initiation of ICI | Best Response to ICI | Length of Time on PD-1/PD-L1 Therapy Until Development of Pericarditis | Other irAEs | Therapy and Outcome | Histopathologic Findings |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Carboplatin + Pemetrexed + Bevacizumab × 3 cycles | Palliative RT to the right lung hilum (30 Gy) and right hip | PD-L1 inhibitor | 14 days | Partial response (RECIST v1.1) | 78 days | None | Presented with cardiac tamponade, and had cardiac arrest, did not respond to resuscitation and died | Complete pathologic response in hilar, carinal lymph nodes, right upper lobe of liver and pancreas, residual viable tumor identified in the left adrenal gland<br>Cytology negative for malignant cells in pericardial effusion |
| 2 | Carboplatin + Pemetrexed × 6 cycles followed by Pemetrexed maintenance | Palliative RT (44 Gy) to right lung upper lobe | PD-L1 inhibitor + CTLA-4 inhibitor | 145 days | Partial response (RECIST v1.1) | 131 days | Grade 2 hypothyroidism (day 42) | Received pericardial drainage and pacemaker for arrhythmias, experienced further clinical decline, and died 13 days after her presentation | Complete pathologic response in bilateral lung, periportal and peripancreatic LNs, only residual disease limited to thyroid gland (contiguous dissemination) |
| 3 | Cisplatin + Pemetrexed + Multikinase TKI × 6 cycles, followed by Pemetrexed + TKI | No prior RT | PD-L1 inhibitor | N/A | Stable disease | 98 days[a] | None | Received pericardial window, with symptomatic improvement, PD after further 3 months of therapy with no additional toxicity after reintroduction | |

[a]Trace pericardial effusion noted in an imaging study after 60 days of therapy.
RT, radiation therapy; ICI, immune checkpoint inhibitor; PD-1, programmed death 1; PD-L1, programmed death ligand 1; irAE, immune-related adverse event; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; PD, progressed disease; LN, lymph node.

antigen and a homologous heart tissue, and antitumor activity in the setting of a malignant pericardial or myocardial involvement.[10] In addition, the observations in animal models suggest importance of the CTLA-4 and PD-1 pathways in limiting T cell–mediated inflammation in the heart.[11,12] The role of PD-1/PD-L1 has been studied in cardiac ischemia-reperfusion injury and myocardial infarction models, which showed increased protein expression of PD-1 and PD-L1 in cardiomyocytes in isolated ischemic-reperfused rat hearts.[13] This may be particularly important in patients with pre-existing cardiac conditions. Another relevant concern in lung cancer patients is the role of the T cell–mediated injury secondary to radiation. In preclinical models it has been shown that PD-1 modulates radiation-induced cardiac toxicity through cytotoxic T lymphocytes, and an increased mortality with combination of cardiac irradiation and anti–PD-1 antibody has been observed in animal models.[14] Because acute pericarditis can be secondary to viral infections or connective tissue disease in immunotherapy-naïve patients, immune checkpoint blockade can theoretically flare subclinical presentations of etiologies as well.[15,16]

In case 1, one possible etiology for the patient's fibrinous pericarditis is an exuberant immune response by the CD8+ cytotoxic T cells, facilitated by the anti–PD-L1 treatment during pericardial inflammation secondary to radiotherapy (case 1 underwent right lung radiation with the overlapping cardiac structures in the radiation field [Fig. 1]). For the same case, another consideration is a possible contribution to his pre-existing cardiac comorbidities. At autopsy the slices of the heart showed impressive left ventricular hypertrophy, probably indicative of sustained hypertension (Fig. 2*B*). Another potential mechanism of the pericardial injury is the antitumor response to a metastatic involvement in the pericardium; however, in our patient cohort two autopsy cases (cases 1 and 2) were both in myocardium and in pericardium, whereas in case 3 the pericardium and the smears of the sanguineous fluid in the pericardial cavity did not contain any malignant cells. Mechanisms for immune-mediated pericardial damage can be multifactorial. In our series, the lower expression of granzyme B in the pericardium infiltrating T cells suggests that although cytotoxic T cells may still be involved in toxicity (which is supported by the comparable levels of CD8 expression across sites), the mechanism might differ and may not be granule exocytosis–mediated. Other cytokines or even death ligands expressed or released by cytotoxic T cells, such as FasL, and TRAIL can play a role in toxicity. Our study assessment of the macrophage population across sites revealed a uniformly higher

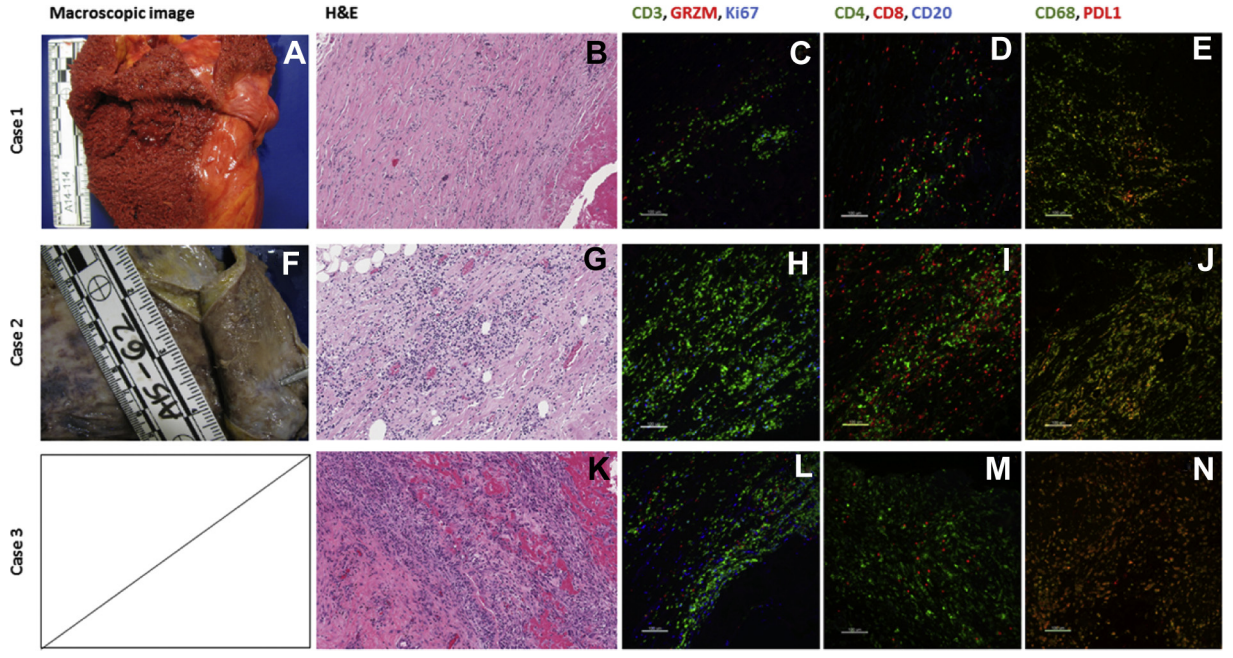


**Figure 3.** First, second, and third rows are macroscopic, hematoxylin and eosin (H&E) stained images, and tumor-infiltrating lymphocytes (TILs) multiplexing images from cases 1, 2, and 3, respectively. The first column (*A* and *F*) shows macroscopic images from a pericardial sample for cases 1 and 2. The second column (*B*, *G*, and *K*) shows H&E images of the pericardial samples (original magnification ×10). The third column (*C*, *H*, and *L*) represents multiplexing with CD 3 (*green*), granzyme (*red*), and Ki 67 (*blue channel*). The fourth column (*D*, *I*, and *M*) represents multiplexing with CD4 (*green*), CD8 (*red*), and CD20 (*blue*). The fifth column (*E*, *J*, and *N*) represents CD68 (*green*) and programmed death ligand 1 (PD-L1) (*red*).

CD68+ expression in the pericarditis samples. This raises the question of whether PD-1/PD-L1–targeted treatment dysregulates the macrophage function leading to excess activity in specific organs. Cardiotoxicity is a rare but potentially fatal complication associated with immunotherapy; pathogenesis is not well known, and diagnostic criteria are lacking.[4] Prospective studies will be helpful to identify risk factors, mechanism, and preventions. Additional caution is needed for patients who have underlying autoimmune disease and/or exposure to radiation therapy before immunotherapy. A high index of suspicion and a low threshold for investigation should be applied in cases of cardiovascular symptoms in patients with immune checkpoint therapy.

## Acknowledgments

This work was supported by funds from the Yale SPORE in Lung Cancer P50-CA196530, the Yale Cancer Center CCSG grant P30-CA016359 and by Stand Up To Cancer - American Cancer Society Lung Cancer Dream Team Translational Research Grant SU2C-AACR-DT17-15.

## Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2019.02.026.

## References

1. Gibson R, Delaune J, Szady A, Markham M. Suspected autoimmune myocarditis and cardiac conduction abnormalities with nivolumab therapy for non-small cell lung cancer. *BMJ Case Rep*. 2016;2016:pii bcr2016216228.
2. Läubli H, Balmelli C, Bossard M, Pfister O, Glatz K, Zippelius A. Acute heart failure due to autoimmune myocarditis under pembrolizumab treatment for metastatic melanoma. *J Immunother Cancer*. 2015;3:11.
3. Neilan TG, Rothenberg ML, Amiri-Kordestani L, et al. Myocarditis associated with immune checkpoint inhibitors: an expert consensus on data gaps and a call to action. *Oncologist*. 2018;23:874–878.
4. Escudier M, Cautela J, Malissen N, et al. Clinical features, management, and outcomes of immune checkpoint inhibitor-related cardiotoxicity. *Circulation*. 2017;136:2085–2087.
5. Wang DY, Salem JE, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Oncol*. 2018;4:1721–1728.
6. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol*. 2018;71:1755–1764.
7. Yun S, Vincelette ND, Mansour I, Hariri D, Motamed S. Late onset ipilimumab-induced pericarditis and pericardial effusion: a rare but life threatening complication. *Case Rep Onocol Med*. 2015;2015:794842.
8. Goldstraw P, Chansky K, Crowley J, et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11:39–51.
9. Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann Oncol*. 2015;26:2375–2391.
10. Johnson DB, Balko JM, Compton ML, et al. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med*. 2016;375:1749–1755.
11. Lucas JA, Menke J, Rabacal WA, Schoen FJ, Sharpe AH, Kelley VR. Programmed death ligand 1 regulates a critical checkpoint for autoimmune myocarditis and pneumonitis in MRL mice. *J Immunol*. 2008;181:2513–2521.
12. Love VA, Grabie N, Duramad P, Stavrakis G, Sharpe A, Lichtman A. CTLA-4 ablation and interleukin-12 driven differentiation synergistically augment cardiac pathogenicity of cytotoxic T lymphocytes. *Circ Res*. 2007;101:248–257.
13. Baban B, Liu JY, Qin X, Weintraub NL, Mozaffari MS. Upregulation of programmed death-1 and its ligand in cardiac injury models: interaction with GADD153. *PloS One*. 2015;10, e0124059.
14. Du S, Zhou L, Alexander GS, et al. PD-1 modulates radiation-induced cardiac toxicity through cytotoxic T lymphocytes. *J Thorac Oncol*. 2018;13:510–520.
15. LeWinter MM. Clinical practice. Acute pericarditis. *N Engl J Med*. 2014;371:2410–2416.
16. Toi Y, Sugawara S, Sugisaka J, et al. Profiling preexisting antibodies in patients treated with anti-PD-1 therapy for advanced non-small cell lung cancer. *JAMA Oncol*; 2018. https://doi.org/10.1001/jamaoncol.2018.5860.