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CASE REPORT: CLINICAL CASE SERIES

Myocardial and Pericardial Toxicity Associated With Immune Checkpoint Inhibitors in Cancer Patients

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ABSTRACT

We recount a single-center experience with cardiac immunity-related adverse effects in patients treated with immune checkpoint inhibitors. Of 2,830 patients, 9 patients (0.3%) developed cardiac immunity-related adverse effects (4 cases of cardiomyopathies, 2 of myocarditis, 2 of acute pericarditis, and 1 of large pericardial effusion). Disease profiles, hospital courses, and outcomes are reported. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2020;2:191–9)

Antitumor activity of immune checkpoint blockers (ICI) is mediated through modulation of the inhibitory pathway in T cells, promoting immune cells to invade tumor cells (1). ICIs emerged a decade ago as a novel therapy in the management of several advanced malignancies. However, ICIs are associated with a wide spectrum of immunity-related adverse effects (IRAEs) that can affect multiple organ systems. Common IRAEs include dermatological issues, endocrinopathies, neuropathies, and colitis; whereas others such as cardiotoxicity, musculoskeletal problems, hematological complications, venous thromboembolism, and pulmonary toxicity are less well recognized (2–5). In particular, the severity of ICI-associated cardiotoxicities varies from mild to life threatening; several cases of fatal cardiotoxicity have been reported (6). With the increasing use of ICIs, this study sought to describe the contemporary incidence of ICI-associated cardiotoxicities in real-world clinical practice in a large integrated health care system.

CASE IDENTIFICATION

POPULATION. This is a case series of patients who developed cardiac IRAEs while taking ICIs. Consecutive patients older than 18 years of age who received an ICI at the Cleveland Clinic between 2011 and 2018 and developed pericardial or myocardial toxicity as an IRAE were included. The ICIs investigated were anti-programed cell death receptor-1 (anti-PD-1) (nivolumab, pembrolizumab), anti-programmed cell death ligand-1 (PDL-1) (atezolizumab, avelumab, and durvalumab), and anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibodies (ipilimumab, tremelimumab). Cardiac IRAEs were included if they occurred after the start of the ICI therapy, and there was no

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Informed consent was obtained for this case.

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ABBREVIATIONS AND ACRONYMS

CTLA = cytotoxic T-lymphocyte-associated antigen

ECG = electrocardiogram

ICI = immune checkpoint inhibitors

IRAE = immunity-related adverse effects

PD = programmed cell death receptor

PDL = programmed cell death ligand

similar history, and after exclusion of other secondary causes by a cardiologist.

DEFINITIONS. The diagnosis of acute myocarditis was believed to be highly likely if the patient satisfied the clinical presentation criteria along with 2 other criteria (electrocardiography, imaging, and laboratory test results), according to the 2013 position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases (7). Note that Bonaca et al. (8) recently proposed a new definition for immunotherapy-induced myocarditis. Under their criteria, case 6 (Table 1) would have a diagnosis of definite myocarditis and the 5 other patients (classified in this paper as cardiomyopathy and myocarditis) probable myocarditis (8). A confirmatory endomyocardial biopsy was avoided in patients with end-stage cancer in order to increase comfort (2). Acute pericarditis was diagnosed according to 2015 European Society of Cardiology Guidelines for the diagnosis and management of pericardial diseases (9). Disease profile, hospital course, and outcomes were studied.

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LEARNING OBJECTIVES

- Cardiac IRAEs may have atypical presentations, and early detection needs systemic surveillance in patients taking ICIs, and the involvement of a cardiologist or cardio-oncologist.
- Myocarditis due to ICIs can occur with or without: 1) electrocardiogram changes; 2) cardiomyopathy; 3) elevated troponin concentrations; or 4) elevated N-terminal pro-B-type natriuretic peptide levels.
- There is an association between cardiac IRAEs and other noncardiac IRAEs, particularly myocarditis and myasthenia gravis.
- It is important to rule out other causes of myocardial and pericardial diseases, especially ischemic cardiomyopathy and malignant effusions. The spontaneous resolution of the cardiac findings after withholding the medication is common in the case of ICI-induced cardiotoxicity and unlikely if the cause is malignant or ischemic.
- The lack of data can be identified in the role of early high-dose steroids and the concerning mortality rate of myocarditis.

CASE DESCRIPTION. Baseline characteristics. Of 2,830 consecutive patients in whom ICI therapy was initiated, 9 patients developed myocardial or pericardial toxicity. The mean age was 70 ± 9 years, 55% were males, and 33% were nonwhite. Of the 9 patients with IRAEs, 5 had lung cancer (3 adenocarcinomas and 1 non-small cell cancer), 2 had melanomas (1 cutaneous and 1 anorectal), 1 had cutaneous squamous cell carcinoma, and 1 had prostate adenocarcinoma. Patients received monotherapy with an ICI, except for case 1, who received 2 months of a combination ipilimumab and nivolumab followed by monotherapy with nivolumab. The median time from initiation of immunotherapy to the onset of cardiac IRAE was 70 days. The Naranjo score, which estimates the probability of an adverse drug reaction (10), was found to be between 4 and 6, indicating a probable causal relationship between the drug and the cardiac side effect. Progression of disease was observed in 2 patients; 2 other patients could not be assessed for progression because they died within a week. Immunotherapy was reintroduced in only 1 patient (Table 1, case 7) who had pericarditis after the medication was withheld and high-dose steroids were administered. In that case, the patient's cancer was responding adequately to treatment, so the benefit of immunotherapy was believed to be superior to the risk of recurrent pericarditis. Most patients had other associated IRAEs such as colitis, pancreatitis, hepatitis, hypothyroidism, myasthenia gravis, myositis, and pneumonitis.

Cases of cardiomyopathy. Four patients had cardiomyopathy attributed to the ICIs (Table 1, cases 1 to 4). All patients had advanced cancer (stages III and IV melanomas and lung adenocarcinomas). Immunotherapy was the first-line therapy in case 2, due to advanced disease and immunohistochemistry results positive for PDL-1 in 99% of tumor cells. All patients presented with shortness of breath on exertion, and 2 of them had additional chest tightness. Troponin T concentration was not elevated (however, high-sensitivity troponin T was not used), but N-terminal pro-B-type natriuretic peptide concentrations were high in cases 2 and 4 [Table 1], although it was not available in the others). All patients had systolic dysfunction with left ventricular hypokinesia: cases 2 and 4 had a drop in their ejection fraction (Table 1); and cases 1 and 3 had no prior echocardiography for comparison. Ischemic cardiomyopathy was ruled out in cases 1 to 3 (Table 1) by stress test and left heart catheterization. Case 4 was considered less likely to have ischemic cardiomyopathy because echocardiography showed global hypokinesia on admission and systolic function was recovered after withholding the immunotherapy (Video 1). Systolic function was not

recovered in case 2 (Table 1) after withholding the medication. Death occurred in 1 patient (case 3) 44 days after admission with cardiomyopathy.

Cases of acute myocarditis. Two patients had acute myocarditis (Table 1, cases 5 and 6) due to pembrolizumab. Case 5 had locally advanced cutaneous squamous cell carcinoma, and case 6 had Stage IV prostate adenocarcinoma. Case 5 received pembrolizumab as the first-line therapy. Both patients presented with eye ptosis, generalized weakness, and fatigue, and both were proven to have concomitant myasthenia gravis and autoimmune myositis due to pembrolizumab. In case 5, the electrocardiogram (ECG) showed atrial fibrillation without any ST- and T-segment changes; troponin T (not high sensitivity) concentration was 2.36 ng/ml (normal is <0.029 ng/ml), and an echocardiogram showed low ejection fraction of 36% with global hypokinesia. Ischemic cardiomyopathy was deemed unlikely given the global nature of the hypokinesia, the absence of ischemic changes on electrocardiogram, the lack of chest pain, and the presence of other associated autoimmune conditions due to pembrolizumab. In case 6 (Table 1), the ECG showed ST-segment elevation in lateral leads with reciprocal depression in inferior leads, and troponin T (not high sensitivity) concentration was 5.18 ng/ml. An urgent left heart catheterization procedure revealed a 60% occlusion of the right coronary artery with no other significant lesions. Echocardiography showed an ejection fraction of 60% with no new wall motion abnormalities. The patient was started on prednisone, 60 mg daily. This patient decided to be referred to hospice, and he died 7 days after his initial admission.

Pericardial diseases. Two patients developed acute pericarditis (Table 2, cases 7 and 8), and 1 patient had a large pericardial effusion (case 9). All 3 patients had lung cancer (2 had adenocarcinomas, and 1 had non-small cell lung cancer, stages IIIA and IV) and received nivolumab after chemotherapy and radiation failed. Case 7 presented with typical pericarditis chest pain (pleuritis, relieved on bending forward). Echocardiography showed a new, small circumferential pericardium with an ejection fraction of 58%. His C-reactive protein was 2.41 mg/dl (normal is <1 mg/dl), and his erythrocyte sedimentation rate was 102 mm/h (normal is <10 mm/h). The patient was started on prednisone, 75 mg daily, because of his distressing symptoms and was discharged with a 5-week slow taper of prednisone. His symptoms completely resolved, and a repeated echocardiogram 1 month later showed resolution of his moderate pericardial effusion and improvement of his inflammatory markers. He was restarted on nivolumab 1 month later as his metastatic disease had stabilized with immunotherapy. The patient continues to tolerate the medication well, and he has had no other side effects since. Case 8 (Table 1) presented with typical pericarditis chest pain with additional worsening shortness of breath and cough productive of clear sputum. Three months before the patient's presentation, she was found to have a recurrence of her lung cancer and was enrolled in a clinical trial with the combination nivolumab, tetrahydrouridine, and decitabine. She had a new, small circumferential pericardial effusion 1 month before her presentation that resolved after 2 weeks. Echocardiography originally showed a normal left ventricular ejection fraction of 65% and a moderate pericardial effusion that became large the next day, without evidence of tamponade or constrictive physiology. Her C-reactive protein concentration was 31.3 mg/dl, and her erythrocyte sedimentation rate was 86 mm/h. She was started on colchicine, 0.6 mg daily, and ibuprofen, 400 mg 4 times daily, and her effusion became trivial within 3 days (Figure 1). Steroids were deemed unnecessary because the patient's symptoms and effusion resolved without corticotherapy. Nivolumab was withheld on discharge, and the patient had no recurrence. She died 11 weeks later under hospice care. Case 9 (Table 2) presented with progressive shortness of breath. Computed tomography of the chest displayed bilateral new ground-glass and consolidative opacities. Echocardiography showed a left ventricular ejection fraction of 60% and a new large effusion without tamponade or constriction physiology. The patient was started on prednisone, 80 mg daily for nivolumab-induced pneumonitis, and his large effusion resolved after 1 week. Nivolumab was withheld on discharge, and the patient had no recurrence. He died 2 years later, under hospice care.

DISCUSSION

Cardiotoxicities due to ICIs are rare. The incidence of myocarditis has been reported to be as high as 1% (11,12). Cardiovascular toxicity consists of cardiac fibrosis, cardiac arrest, autoimmune myocarditis, cardiomyopathy, heart failure, pericardial involvement, and vasculitis (13,14). The key finding in the present cohort of real-world clinical practice is the relatively low incidence of ICI-mediated cardiotoxicities (0.32% in the present cohort) and portended poor prognosis, especially if myocarditis developed. Also, cardiomyopathy and pericarditis seem to be more common than myocarditis in terms of cardiac IRAEs. However, many cases are likely missed due to the lack of systemic

TABLE 1 Characteristics of Patients Who Developed Cardiomyopathy and Myocarditis Due to Immune Checkpoint Inhibitors

Case	Age, yrs, Sex, Race, Weight	Cardiac IRAE	Primary Cancer and Mutations	Other Medical History	Cancer Stage Before Immunotherapy	Immunotherapeutic Agent	Onset of Cardiac IRAE	Other Cancer Treatment (Chemotherapy, Immunotherapy, Radiation Therapy or Surgical Therapy)	Clinical Presentation	Electrocardiogram/ Holter/Stress Test Features
1	60, male, white, 101 kg	Cardiomyopathy	Anorectal melanoma, BRAF, NRIS, and KIT-negative.	GERD	III	Ipilimumab/ nivolumab, followed by nivolumab monotherapy	18 months after the first dose and 5 months after the last dose	Surgical resection (twice)	Chest tightness, decreased exercise tolerance	ECG: new incomplete right bundle branch block
2	84, female, black, 82 kg	Cardiomyopathy	Adenocarcinoma of the lungs, EGFR wild type, KRAS Mutant (G12C) BRAF WT, PDL-1 High (99%)	PVD, CAD, HTN	IV	Pembrolizumab monotherapy	38 days after the first dose and 16 days after the last dose	(–)	Shortness of breath	ECG: new T-wave inversions V_4-V_5 and V_6 Stress test: frequent premature ventricular complexes
3	71, female, white, 58 kg	Cardiomyopathy and a small pericardial effusion	Adenocarcinoma of the lung, negative for EGFR and ALK; 20% PD1	Atrial fibrillation, HTN, COPD	IIIC	Durvalumab monotherapy	5 months after the first dose, 9 days after the last dose	Chemotherapy and radiotherapy	Abdominal pain (pancreatitis and ileus), shortness of breath on exertion	ECG: Atrial fibrillation
4	67, male, white, 82 kg	Cardiomyopathy	Cutaneous melanoma, BRAF negative	HTN, asthma	IIIB	Ipilimumab monotherapy	15 months after the first dose and 4 months after the last dose	Multiple local resections, adjuvant interferon alfa-2B	Intermittent chest discomfort and shortness of breath on exertion	Holter: 215 PVBs per hour with PVBs constituting 5.2% of total beats and first-degree AV block
5	80, female, white, 100 kg	Myocarditis	Cutaneous squamous cell carcinoma	Sarcoidosis, atrial fibrillation, CKD stage III, HTN	Locally advanced with single ipsilateral node involvement	Pembrolizumab monotherapy	35 days after the first dose and 15 days after the last dose	(–)	Bilateral eye ptosis, generalized weakness, fatigue	ECG: atrial fibrillation
6	80, male, white, 74 kg	Myocarditis	Prostate adenocarcinoma	HTN, hyperlipidemia	IV	Pembrolizumab monotherapy	30 days after the first dose and 9 days after the last dose	Chemotherapy	Right eye ptosis, generalized weakness, and fatigue.	ECG: ST-segment elevation in leads I and AVL with reciprocal depression in inferior leads

(–) = negative; (+) = positive; Anti-ACRA = anti-acetylcholine receptors antibodies; CAD = coronary artery disease; CK = creatine kinase; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; ECG = electrocardiogram; GERD = gastro-esophageal reflux disease; HTN = hypertension; IRAE = immune related adverse event; PVBs = premature ventricular beats; PVD = peripheral vascular disease; RCA = right coronary artery; WSR = Westergren sedimentation rate.

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surveillance of cardiac IRAEs in this patient population, and this low incidence may be an underestimate.

Although the exact mechanism of cardiotoxicity has yet to be elucidated, histopathological evaluation has revealed $CD4^+$ and $CD8^+$ cells in the myocardium and the conducting system in affected patients. PD-L1 was also highly expressed in the myocardium of those patients. One of the earliest cases of pembrolizumab-induced myocarditis, reported by

TABLE 1 Continued

Troponin T Elevation	Inflammatory Markers, proBNP/ NT-proBNP, Other Relevant Laboratory Findings	New Structural Abnormality on Echocardiography	Stress Test or Left Heart Angiography	Treated With High-Dose Steroids	Recovery	Naranjo Score	Recurrence of Side Effect	Associated IRAEs	Progression of Primary Malignancy	Death/Cause of Death
(–)	CRP: 2.41 mg/dl WSR: 22 mm/h	Low ejection fraction of 26% with global hypokinesia	Nuclear stress test normal	Prednisone 60 mg daily received for colitis then tapered dose	Yes, repeat ejection fraction 40% after holding medication and continuing steroids	5	(–)	Colitis, pancreatitis, arthritis	(–)	(–)
(–)	NT proBNP: 4.683 pg/ml	A drop of ejection fraction from 60% to 35% with global hypokinesia	Exercise stress test normal	(–)	Symptoms improved on heart failure treatment; however, ejection fraction still 35%	4	(–)	(–)	(–)	(–)
(–)	Unavailable	Low ejection fraction of 30%, global hypokinesia except preserved apical wall motion	A left heart catheterization showed 25% to 30% plaque in some of the distal coronaries	Prednisone 40 mg daily	Yes, repeat ejection fraction was 50% after holding drug and starting steroid	5	(–)	(–)	(+), pancreatic metastasis	(+), non-cardiac after 44 days
(–)	NT-proBNP: 637 pg/ml	Drop of ejection fraction from 59% to 44% with new global hypokinesia	(–)	(–)	Yes, repeat ejection fraction 56% after holding medication and starting carvedilol	5	(–)	Hepatitis and hypothyroidism	(–)	(–)
Troponin T: 2.36 ng/ml	CRP: 5.9 mg/dl CK: 1,519 U/l AST: 308 U/l ALT: 254 U/l	Low ejection fraction of 36% with global hypokinesia	(–)	Prednisone 100 mg daily	Non-applicable, the patient died 4 days later	4	Non-applicable, the patient died 4 days later	Myasthenia gravis, hepatitis, and myositis	Non-applicable, the patient died 4 days later	(+), cardiac, after 4 days, in hospice.
Troponin T: 5.18 ng/ml	proBNP: 13,118 pg/ml (was 590 pg/ml 2 yrs back) CK: 1,835 ng/ml Aldolase: 33.5 U/l, Anti-ACRA: positive	No, ejection fraction 60% with no new wall motion abnormalities	Yes, an urgent left heart catheterization showed a 60% occlusion of the RCA	Prednisone 60 mg daily	Non-applicable, the patient died 7 days later	5	Non-applicable, the patient died 7 days later	Myositis, myasthenia gravis	Non-applicable, the patient died 7 days later	(+), non-cardiac, after 7 days, in hospice

Läubli et al. (15), also demonstrated predominant infiltration of $CD8^+$ cells on myocardial biopsy. In experimental studies in mice, fatal myocarditis/cardiomyopathy were common in the gene-deleted PD-1 myocardium (16,17). PD-L1 expressed in human myocardium is involved in the protection from immune-mediated cardiac injury and inflammation (18).

In the present case series, 9 cases of cardiomyopathy, myocarditis, pericarditis, and pericardial effusions were described. Most presentations were atypical, and most patients had other associated IRAEs. None of the patients had a history of other autoimmune diseases. The 2 patients with myocarditis presented with symptoms of myasthenia gravis (ocular symptoms) and myositis (proximal muscle

TABLE 2 Characteristics of Patients Who Developed Acute Pericarditis and Pericardial Effusion Due to Immune Checkpoint Inhibitors

Case #	Age (yrs), Sex, Race, Weight	Cardiac IRAE	Primary Cancer with Positive Markers	Previous History	Stage of Cancer Before Immunotherapy	Immunotherapeutic Agent	Onset of Cardiac IRAE	Other Cancer Treatment (Chemotherapy, Immunotherapy, Radiation Therapy or Surgical Therapy)	Clinical Presentation	Typical Pericarditis Chest Pain
7	70, male, white, 110 kg	Acute pericarditis	Adenocarcinoma of the lung, EGFR wild type	Rheumatic heart disease, hypertension, diabetes mellitus, chronic kidney disease, and obstructive sleep apnea	IV	Nivolumab monotherapy	13 weeks after the first dose and 2 weeks after the last dose	Chemotherapy and radiotherapy prior	Pleuritic chest pain	(+)
8	60, female, black, 57 kg	Acute pericarditis	Adenocarcinoma of the lung, markers negative	COPD, recurrent PE, and hypertension	IIIA	Nivolumab + THU-Decitabine as part of a clinical trial	9 weeks after the first dose and 3 weeks after the last dose	Chemotherapy and radiotherapy prior	Pleuritic chest pain, worsening shortness of breath, cough productive of clear sputum	(+)
9	58, male, black, 80 kg	Large pericardial effusion	Non-small cell lung cancer, EGFR wild type	Peptic ulcer disease	IV	Nivolumab monotherapy	10 weeks after the first dose and 2 weeks after the last dose	Chemotherapy and radiotherapy prior	Progressive shortness of breath	(–)

NT-proBNP = N-terminal pro-B-type natriuretic peptide; PE = pulmonary embolism; THU = tetrahydrouridine; other abbreviations as in Table 1.

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weakness) predominantly, with generalized weakness and fatigue as the only clues for associated myocarditis. The 4 other patients with cardiomyopathy presented with shortness of breath at exertion but also with chest pressure and symptoms of autoimmune pancreatitis. In addition to the typical pleuritic chest pain, the 2 patients with acute pericarditis manifested other respiratory symptoms (e.g., shortness of breath and productive cough) that might have been due to their lung cancer or associated autoimmune pneumonitis. Thus, there should be a very low level of suspicion for a cardiac IRAE when a patient presents clinically with other IRAEs or atypical symptoms. This may warrant screening with echocardiography (for pericardial effusion, constriction physiology, systolic function, and wall motion abnormalities) and cardiac enzyme levels (for myocarditis and to rule out an acute coronary syndrome) to rule out cardiac involvement. Because the 2 patients with myocarditis had associated myasthenia gravis and myositis at the time of presentation, there may be a common autoimmune mechanism that preferentially affects receptors of the striated muscles. The fatality rate among the present patients with myocardial toxicity was estimated to be 50% (3 of 6 patients died within 2 months after diagnosis).

The time from initiation of ICI and presentation for cardiac IRAEs varies from 1 to 18 months and does not necessarily occur after the first dose. Earlier presentation (within 1 month of starting therapy in this report) was seen in patients presenting with myocarditis, consistent with prior work (12). Moslehi et al. (6) reported 101 cases of immunity-mediated severe myocarditis from VigiBase, the World Health Organization database (19). Of 101 patients, 57% were taking anti-PD1 monotherapy; most of those patients were reported to have early onset myocarditis (after 1 or 2 doses of treatment). Pericardial involvement was seen only with nivolumab therapy, and all patients had lung cancer. The association between lung cancer and pericardial involvement due to ICIs (also elicited by Salem et al. [14]) is not fully understood.

Both patients with myocarditis died within 1 week, reflecting the poor prognosis of ICI-mediated myocarditis. This is consistent with a

TABLE 2 Continued

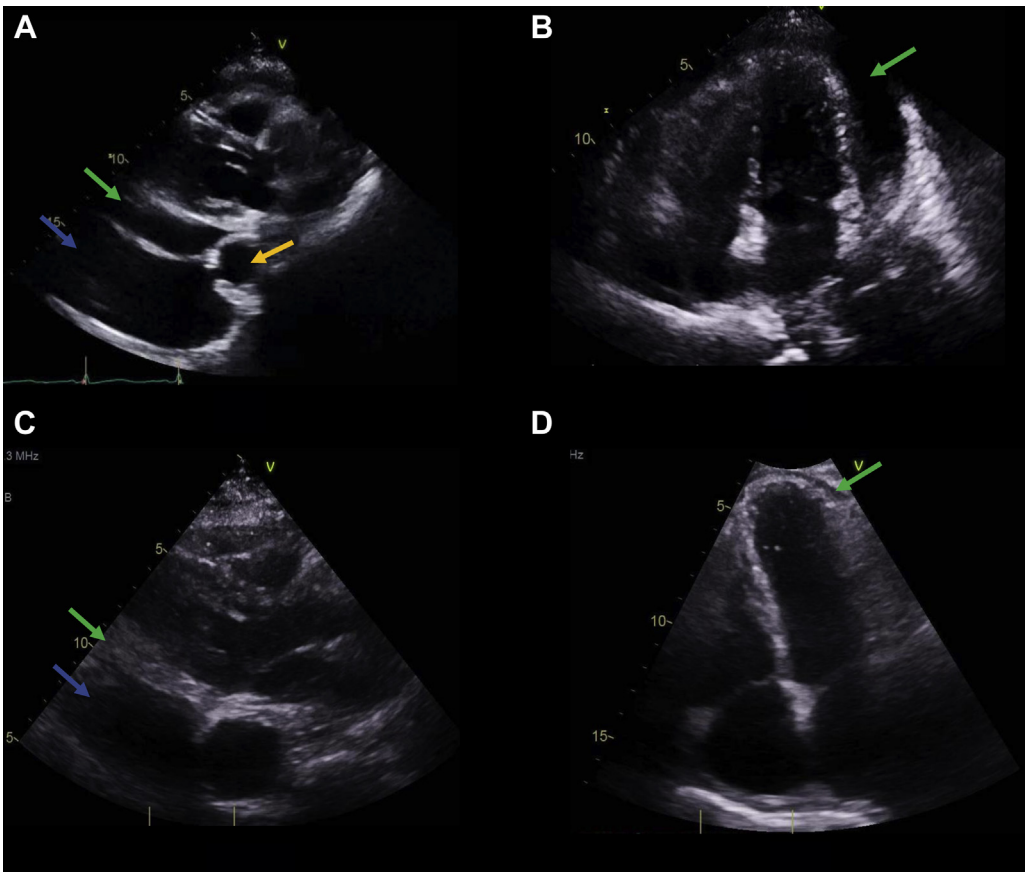
Typical ECG Changes of Pericarditis	Presence of Pericardial Rub	Echocardiography Findings: New or Worsening Effusion, Evidence of Tamponade or Constriction	Exclusion of Malignant Effusion	Inflammatory Markers, Troponin T and proBNP/ NT-proBNP	Treated with High-Dose Steroids	Recovery	Naranjo Score	Recurrence of Side Effect	Associated IRAE	Progression of Primary Malignancy	Death/Cause of Death
(+)	(–)	New small circumferential pericardial effusion, no evidence of tamponade or constriction	Tap not done, however, effusion responded to steroids	CRP: 7.1 mg/dl WSR:102 mm/h NT-proBNP: 855 pg/ml Troponin T negative	Prednisone 75 mg daily then tapered	Yes, after holding medication and starting steroids	4	(–), even after drug reintroduced 5 weeks later	(–)	(–)	(–)
(–)	(–)	Yes, worsening circumferential large pericardial effusion measuring 2 cm, no evidence of tamponade or constriction. Large pleural effusion	Tap not done, however, effusion responded to colchicine and ibuprofen	CRP: 31.3 mg/dl WSR: 86 mm/h Troponin T negative NT-proBNP: 1,051 pg/ml	(–)	Yes, on colchicine and ibuprofen	6	(–)	(–)	(–)	(+), non-cardiac, after 11 weeks, was on hospice
(–)	(–)	Yes, new large pericardial effusion, no evidence of tamponade or constriction	Tap not done, however, effusion responded to steroids	Not measured	Prednisone 80 mg daily then tapered	Yes, after holding the medication and starting steroids	5	(–)	Pneumonitis	(+)	(+), non-cardiac, after 13 months, was on hospice

recent study which found that major adverse cardiac events occurred in 46% of cases of myocarditis due to ICIs (12). It should be noted that the cause of death was likely cardiac in case 5 only, due to onset of atrial fibrillation and respiratory failure during the hospital stay. Having a normal ejection fraction (as in case 6) is not uncommon and occurs in 38% of fulminant myocarditis. Immunity-mediated fatal myocarditis has also been reported in patients treated with the combined therapy with ipilimumab and nivolumab (11). Regarding the patients with cardiomyopathy, all except 1 recovered their systolic function after withholding the medication. This 1 patient was not treated with high-dose steroids during his hospital admission, and that might have been the reason for lack of full recovery. There was no recurrence of the cardiomyopathy after withholding the medication after discharge. Pericardial involvement had a better prognosis than myocarditis, consistent with published reports (50% mortality in myocarditis versus 21% in pericardial involvement) (14). Steroids were not needed in 1 case of acute pericarditis, and pericarditis did not recur in the other patient with acute pericarditis after reintroduction of nivolumab. Overall, 5 patients had no progression of their primary malignancy, 2 had progression, and the remaining 2 had a fatal outcome during the admission.

For the best outcome after presentation with a cardiac IRAE, the American Society of Clinical Oncology clinical practice guidelines for the management of IRAEs in patients treated with ICI therapy recommends high-dose corticosteroids (1 to 2 mg/kg prednisone) for high-grade cardiovascular IRAEs, and management should be multidisciplinary, with the involvement of a cardiologist or cardio-oncologist and an immunity oncologist (20). Infliximab, mycophenolate, antithymocyte globulin, and abatacept have been tried, although their benefits are still uncertain (11,21–24).

LIMITATIONS. First, the sample size is small. Second, myocardial biopsy, cardiac magnetic resonance imaging, and pericardial drainage were not performed in these patients to confirm the diagnosis or completely exclude a malignant cause. However, the course of the disease and quick recovery of the pericardial effusion made a malignant cause less likely. Third, the patients' presentations were confounded by the concurrence of other IRAEs. Furthermore, there was no systemic evaluation or surveillance for cardiac IRAEs in these patients, which may have led to underdiagnosis.

FIGURE 1 Spontaneous Resolution of Large Pericardial Effusion After 3 Days of Ibuprofen and Colchicine Therapy (Case 8)



Echocardiography parasternal long view **(A and C)** and 4-chamber views **(B and D)**. On presentation **(A and B)**: large circumferential pericardial effusion **(green arrows)** and large pleural effusion **(blue arrow)**. The descending aorta **(orange arrow)** helps to differentiate the 2 effusions. At 2 days after presentation **(C and D)**: spontaneous resolution of pericardial effusion **(green arrows)** and persistence of pleural effusion **(blue arrow)**.

CONCLUSIONS

Pericardial and myocardial involvement is an uncommon side effect of ICIs in real-world clinical practice, and cardiomyopathy and pericarditis seem to be more common than myocarditis. Myocarditis, particularly, can be life threatening. Most of these patients had other associated IRAEs, and both of the patients with myocarditis were diagnosed with myasthenia gravis during the same admission. Given the atypical presentations, systemic evaluation and surveillance for cardiac IRAEs in patients taking ICIs should be implemented in hospitals and emergency rooms to avoid underdiagnosis and for earlier detection, and involvement of a cardio-oncologist or cardiologist is crucial for further investigations and evaluations to better understand the pathophysiology of those diseases and guide management. High-dose steroids are currently indicated in severe cardiac involvement and should not be delayed; however, their effectiveness should warrant further investigations.

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APPENDIX For a supplemental video, please see the online version of this paper.