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CASE REPORT

Myocarditis associated with immune checkpoint inhibitor therapy: a case report of three patients

Kianoush Ansari-Gilani[1] · Sree Harsha Tirumani[1] · Daniel A. Smith[1] · Ariel Nelson[2] · Asrar Alahmadi[2] · Christopher J. Hoimes[2] · Nikhil H. Ramaiya[1]

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Abstract

Immune checkpoint inhibitor (ICI)-associated myocarditis is a rare but potentially fatal complication associated with development of other immune-related adverse events (irAEs). Troponin levels, ECG, echocardiography, and cardiac MR can assist with the diagnosis of this rare albeit serious adverse effect related to immunotherapy. In this case report, we present the clinical and radiological features of myocarditis in three patients presenting with acute symptoms while receiving therapy with ICIs. Blood troponin and ECG were abnormal in all three myocarditis cases. Initial echocardiography was abnormal in two patients with reduced left ventricular ejection fraction (LVEF). The third patient demonstrated an initially normal LVEF with subsequent transient decrease in LVEF on follow-up echocardiogram. Cardiac MR was abnormal in three cases with areas of mid-myocardial/epicardial delayed enhancement. All patients experienced additional irAEs. One patient died shortly after myocarditis diagnosis, one was made comfort care due to poor clinical status, and one improved with steroid treatment.

Keywords Myocarditis · Immune check inhibitors · Immune-related adverse events

Introduction

Immune checkpoint inhibitors (ICIs) are a novel category of drugs that promote immune system-mediated recognition and targeting of cancer cells [1]. ICI-induced T cell activation not only targets cancer cells but also produces a range of autoimmune toxicities [2]. These immune-related adverse events (irAEs) have been described involving the neurological, endocrine, pulmonary, gastrointestinal, cardiovascular, and renal systems.

Myocarditis is an uncommon but potentially fatal complication of treatment with ICIs [1]. This clinically important side effect is likely the most important pathology in major adverse cardiac event (MACE) that has been reported in patients receiving ICIs [3]. Description of myocarditis as a side effect of ICIs is relatively new in the literature, with more reports being published recently [3–5].

This case report presents clinical and radiological data gathered from three patients diagnosed with myocarditis associated with ICI therapy (Table 1). The diagnosis of acute

✉ Daniel A. Smith
Daniel.Smith3@UHhospitals.org

Kianoush Ansari-Gilani
kianoush.ansarigilani@uhhospitals.org

Sree Harsha Tirumani
SreeHarsha.Tirumani@UHhospitals.org

Ariel Nelson
Ariel.Nelson@UHhospitals.org

Asrar Alahmadi
Asrar.Alahmadi@UHhospitals.org

Christopher J. Hoimes
Christopher.Hoimes@UHhospitals.org

Nikhil H. Ramaiya
Nikhil.Ramaiya@UHhospitals.org

[1] Department of Radiology, University Hospital Cleveland Medical Center, 11100 Euclid Avenue, Cleveland, OH 44106, USA

[2] Department of Medicine Division of Hematology and Oncology, University Hospitals Cleveland Medical Center, Case Western Reserve University, Cleveland, OH 44106, USA

Table 1 Clinical and radiological features of immune checkpoint inhibitor-associated myocarditis in 3 patients

	Case 1	Case 2	Case 3
Age	83	78	81
Gender	Male	Female	Male
Cancer type	Renal cell carcinoma	Metastatic melanoma	Metastatic melanoma
Immune check point inhibitor/number of doses	Nivolumab/2	Nivolumab/1 Ipilimumab/1	Nivolumab/1 Ipilimumab/1
Clinical presentation	Abdominal pain, right-sided facial droop, and diffuse weakness	Blurry vision, malaise, and dysphagia	Watery diarrhea, chest pain, and frequent PVC
Days since the start of treatment and diagnosis of myocarditis	28	18	25
Days since the start of treatment to peak troponin	28	25	26
Disease status at time of myocarditis	Stable disease	Stable disease	Stable disease
Treatment stopped/rechallenged	Yes/no	Yes/no	Yes/no, history of prior treatment with pembrolizumab in 2017 with no myocarditis
Comorbidities	Hypothyroidism and hypertension	Hyperlipidemia and depression/anxiety	Hypertension, COPD, and atrial fibrillation
Additional immune-related adverse events	Hepatitis, Bell's palsy, myositis, and encephalitis	Myasthenia gravis, conjunctivitis/uveitis, hepatitis, and myositis	Colitis
Length of admission (days)	3	34	22
Treatment	Steroids	Steroids and plasma exchange	High-dose steroids
Outcome	Cardiac arrest/expired	Pulseless electrical activity, resuscitated, and comfort care	Improved
Cancer status at 16 weeks follow-up	N/A	N/A	Progression
ECG findings	PVCs and ST elevation	T-wave inversion	Frequent PVCs and bradycardia
1st echo after/days	Reduced LVEF: 35%, no regional wall motion abnormality and small pericardial effusion	Normal LVEF: 65%	Reduced LVEF: 45%, no regional wall motion abnormality
Follow-up echo/days	None	Drop in LVEF to 40% after 7 days Normalization of LVEF: 65% after 17 days	Normalization of LVEF: 65% after 14 days
Coronary catheterization	Negative	Negative	Not performed
Initial cardiac MRI	Reduced LVEF: 30% Extensive mid-myocardial and epicardial delayed enhancement (DE) in the septum, inferior, and lateral walls Significant myocardial edema on T2 mapping image in the same areas	Normal LVEF: 65% DE inferoseptal and midseptal and normal	Reduced LVEF: 45% Focal area of DE in base of lateral wall
Follow-up cardiac MRI/days	None	Follow-up MR after 7 days: DE remained the same LVEF dropped to 40%	Follow-up MR after 12 days: same area of DE in base of the lateral wall Stable LVEF: 45%
Troponin (initial, peak)	Initial: 68.49 Peak: 68.49	First: 1.97 Peak: 47.62	First: 1.35 Peak: 1.44

myocarditis for each patient was based on a guideline-recommended scoring system for clinically suspected myocarditis that incorporates several variables, including the clinical, electrocardiographic, biomarker, and imaging features [6].

All patients had a baseline transthoracic echocardiography (TTE) within 6 months prior to treatment which confirmed normal systolic function and left ventricular ejection fraction (LVEF). All patients underwent at least one transthoracic

echocardiography (TTE) during the admission for myocarditis. Cardiac MR (CMR) and coronary catheterization each were performed in all three cases.

Treatment with ICI was stopped in all three cases without rechallenge. All patients were treated with high-dose corticosteroids (methylprednisolone, loading dose of 1 g followed by 1 mg/kg/day), accompanied by plasma exchange in one of the cases. Major cardiac events occurred in two of the three cases.

Case 1

This 83-year-old male with a history of renal cell carcinoma presented with symptoms of abdominal pain, right-sided facial droop, and diffuse weakness shortly after receiving his second dose of nivolumab. ECG on arrival was remarkable for PVCs and ST elevation, with troponin elevated at 68. Initial echocardiogram in this patient with no prior cardiac history demonstrated a reduced left ventricular ejection fraction (LVEF) of 35% and small pericardial effusion without regional wall motion abnormalities. Coronary catheterization revealed no remarkable findings. Cardiac MRI was obtained and demonstrated a reduced LVEF of 30% and extensive mid-myocardial and epicardial delayed enhancement in the septum, inferior, and lateral walls (Fig. 1a and b). Significant myocardial edema was detected on T2 mapping images in the same area (Fig. 1c). Additional immune-related adverse events experienced by this patient included hepatitis, Bell's palsy, myositis, and encephalitis. The patient received steroid therapy while hospitalized for 3 days and subsequently expired during the hospitalization secondary to cardiac arrest.

Case 2

This 78-year-old female with metastatic melanoma presented 18 days after receiving an initial dose of nivolumab and ipilimumab with symptoms of malaise, blurry vision, and dysphagia. Initial echocardiogram demonstrated a normal LVEF of 65%. T-wave inversions were detected on ECG. Initial troponin was measured at 1.97, which ultimately increased to a peak value of 47.62 after 8 days. Cardiac MRI demonstrated delayed enhancement in the inferoseptal and midseptal wall (Fig. 2a and b), while LVEF was preserved. Follow-up CMRs showed no significant change in the distribution and severity of DE, but a decrease in LVEF to 40% was noted. Follow-up echocardiogram after 7 days revealed a transient decrease in the LVEF to 40%, which subsequently normalized on repeat echocardiogram after 17 days. In addition to myocarditis, the patient experienced additional immune-related adverse events, including myasthenia gravis, conjunctivitis/uveitis, hepatitis, and myositis. Coronary catheterization revealed no evidence of significant coronary artery stenosis. The patient was admitted for a 34-day hospital stay in which she received treatment with steroids and plasma exchange. The patient's clinical course was complicated by an episode of pulseless electrical activity with subsequent resuscitation. Ultimately, the decision was made to pursue comfort care measures due to patient's preference and progression of underlying malignancy.

Case 3

This 81-year-old male with a history of metastatic melanoma developed chest pain and watery diarrhea approximately

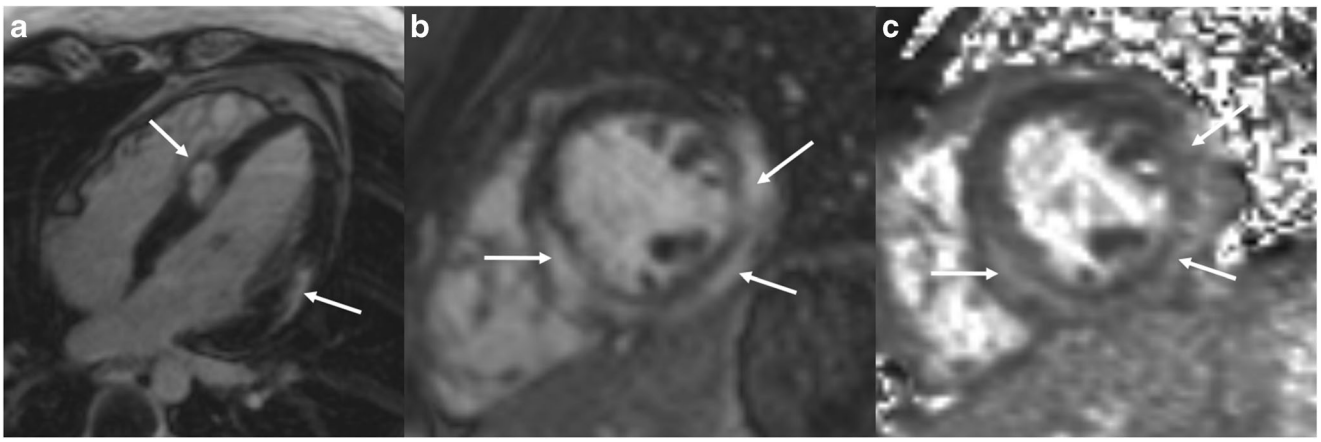

Fig. 1 83-year-old man with metastatic renal cell carcinoma (patient 1), who is being treated with nivolumab and presenting with abdominal pain and diffuse weakness. Post-gadolinium delayed enhancement cardiac MR in 4-chamber (**a**) and short-axis (**b**) views shows large areas of mid-myocardial and epicardial delayed enhancement (DE) seen in the septum, lateral, and inferior walls (arrows) in keeping with areas of scarring. The sub-endocardium is spared. Short-axis T2 mapping image (**c**) shows extensive areas of increased intensity in the same areas (arrows), in keeping with myocardial edema and highly suggestive of myocarditis

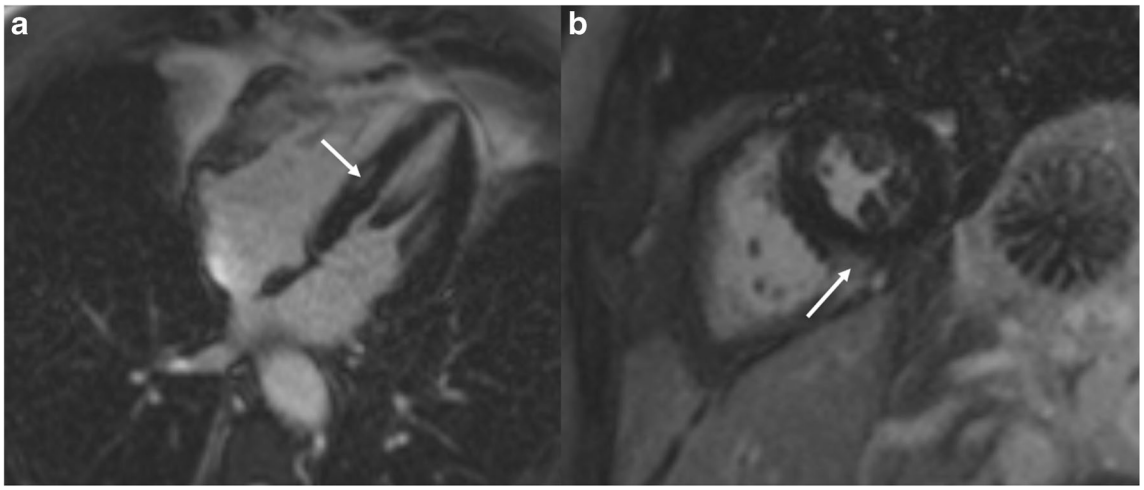

Fig. 2 78-year-old woman with metastatic melanoma (patient 2) who was being treated with nivolumab and ipilimumab presenting with malaise. Post-gadolinium delayed enhancement cardiac MR in 4-chamber (**a**) and short-axis (**b**) views shows areas of mid-myocardial and epicardial delayed enhancement (DE) seen in the septum (arrow in **a**) and inferoseptal wall (arrow in **b**) in keeping with areas of scarring. The sub-endocardium is spared. T2 mapping images were unremarkable (not shown)

25 days after receiving initial doses of nivolumab and ipilimumab. Prior to this, the patient had received immunotherapy with pembrolizumab with no previous episodes of myocarditis. Following presentation, the patient was found to have a newly reduced LVEF of 45% without regional wall motion abnormalities. Initial CMR similarly demonstrated a reduced LVEF of 35% with a focal area of delayed enhancement in the base of the lateral wall (Fig. 3). Follow-up CMR showed no significant change in DE, and LVEF remained reduced. Follow-up TTE after 2 weeks showed improvement in LVEF (65%). The patient also experienced immune-related colitis during his hospital admission. The patient received high-dose steroids for treatment of immune-related myocarditis during the course of his 22-day hospital stay. The patient ultimately improved clinically and was discharged from the hospital. Subsequent follow-up imaging after 16 months demonstrated progression of metastatic disease but no clinical recurrence of myocarditis.

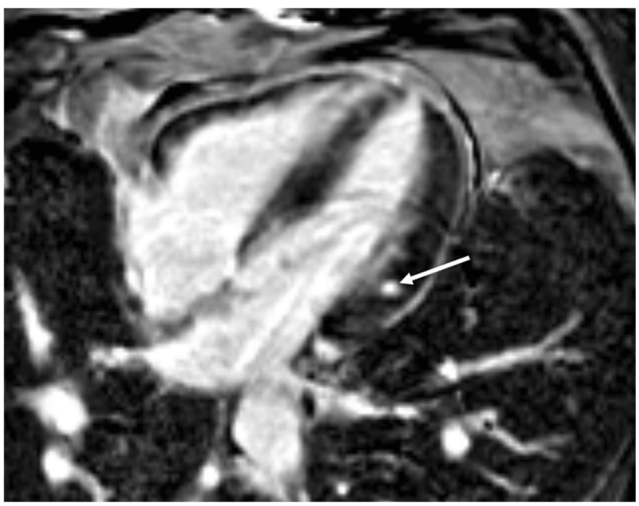

Fig. 3 81-year-old man with metastatic melanoma (patient 3) who was being treated with nivolumab and ipilimumab presenting with chest pain and frequent premature ventricular contractions. Post-gadolinium delayed enhancement cardiac MR in 4-chamber view shows an area of mid-myocardial delayed enhancement (DE) in the lateral wall (arrow) in keeping with an area of scarring. The sub-endocardium is spared. T2 mapping images were unremarkable (not shown)

Discussion

Immune checkpoint inhibitors are being more frequently used in the treatment of malignancies, and the use of ICIs is expected to increase significantly in the coming years. Myocarditis is an uncommon complication of treatment with ICIs. Cardiac myocytes may share targeted antigens with tumors, thus resulting in targeting by activated T cells and subsequent lymphocytic infiltration and myocarditis [4].

The true incidence of ICI-associated myocarditis is not known, but it has been reported to be as low as 0.09% [4] to as high as 1.1% [1]. Due to the relatively low incidence of ICI-associated myocarditis, knowledge of the clinical and radiological features associated with this condition is quite limited.

The three patients included in this case series developed ICI-related myocarditis early in the course of treatment, which is in accordance with prior studies [1]. In two of the cases, myocarditis developed after the first dose of ICI, while in the other patient, myocarditis occurred after the completion of the second dose. All three patients also experienced other irAEs, including myositis, hepatitis, myasthenia gravis, conjunctivitis/uveitis, and colitis.

All three patients were treated with nivolumab either as a single agent or in combination with ipilimumab. Nivolumab has been previously described as an agent commonly triggering ICI-associated myocarditis [1]. In a case series by Mahmood et al., 30% of single-agent treatment ICI-induced myocarditis was caused by nivolumab, while in 75% of combination therapies, nivolumab was present as one of the treatment agents [1].

ECG is a useful inexpensive tool for initial assessment of suspected cases of myocarditis. All three cases showed ECG changes such as ST elevation, T-wave changes, and PVCs. This is in concordance with prior reports about the value of ECG in suggesting the presence of myocarditis [1, 4].

Elevated troponin was present in all three patients. Troponin as a marker of myocyte death, although not specific, is a very sensitive and inexpensive test which can be of great value in suggesting the presence of myocardial injury and myocarditis in the setting of ICI treatment [4]. In case series by Mahmood et al., 94% of cases with myocarditis had elevated troponin levels, and an increase in troponin level to levels > 1.5 ng/ml was associated with four-fold increased risk of myocarditis [1].

Treatment with ICI was discontinued in all three cases after the diagnosis of myocarditis. Resumption after initial discontinuation of ICIs is associated with high rate of recurrent or distinct irAEs and MACE [7]. Treatment with ICI was not rechallenged in any of the cases.

Serious adverse cardiac events occurred in two of our patients. All three patients were treated with high-dose corticosteroids, and in one case, plasma exchange was also performed. Prior studies have demonstrated high-dose corticosteroids and plasma exchange as effective treatment for myocarditis [1, 2, 4].

Echocardiography is typically the initial imaging modality in cases of suspected myocarditis and can provide useful information about myocardial function. While reduced LVEF is commonly seen in the setting of myocarditis, a depressed LVEF at the time of presentation is not a prerequisite for serious cardiac events.

Cardiac MR (CMR) is the imaging modality of choice for assessment of myocarditis [8]. The typical CMR findings in myocarditis include edema and myocardial DE sparing the subendocardial region in a nonischemic distribution [8]. In less severe cases of myocarditis, scarring and DE may be absent [8].

All three of our cases underwent evaluation with CMR during the course of treatment. Reduced LVEF was present in all three cases, but no regional motion abnormality was detected. One case showed myocardial edema on T2 mapping sequence. Delayed enhancement (DE) was abnormal in all CMRs showing areas of scarring in a mid-myocardial and epicardial distribution with sparing of the subendocardial region. Follow-up CMR performed 7 and 14 days after the first CMR in two of the cases did not show any change in the extent, pattern, distribution, and severity of delayed enhancement.

Conclusion

Myocarditis is an uncommon but potentially fatal complication of treatment with ICIs. Diagnostic tools such as blood troponin level, ECG changes, echocardiography, and cardiac MR can help in the diagnosis of ICI-induced myocarditis. Patients usually present with other immune-related adverse events and benefit from high-dose corticosteroid and plasma exchange.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

IRB statement The institutional review board approved the study.

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