JACC: CASE REPORTS VOL. 16, 2023

CASE REPORT

BEGINNER

CLINICAL CASE

Immune Checkpoint Inhibitor-Related Stress Cardiomyopathy

Differential Diagnosis and Key Role of Cardiac Imaging

Lucía Cobarro, MD,[a] Silvia Valbuena-López, MD,[a] Cristina Contreras, MD,[a] Clara Ugueto, MD,[a] Iciar Ruiz-Gutiérrez, MD,[b] Jesús Peña-López, MD,[b] Leticia Ruiz-Giménez, MD,[b] Teresa López-Fernández, MD[a,c]

ABSTRACT

A 76-year-old man with stage IV urothelial carcinoma who was receiving atezolizumab presented with dyspnea, elevated cardiac biomarkers, new negative T waves, and left ventricular apical akinesia. Coronary angiography results were normal. Immune checkpoint inhibitor–related myocarditis was suspected, and high-dose corticosteroid treatment was started. Cardiac magnetic resonance showed apical edema, suggesting stress cardiomyopathy. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2023;16:101881) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 76-year-old man with stage IV upper urinary tract urothelial carcinoma was admitted to the Department of Oncology of La Paz University Hospital, Madrid, Spain, as a result of cough, dyspnea, and fever after his fourth atezolizumab cycle.

LEARNING OBJECTIVES

- To understand the importance of early diagnosis and treatment of cardiac irAEs to minimize cancer treatment discontinuation. Myocarditis is the most feared condition, but other diagnoses should be considered.
- To highlight the importance of evaluating in a multidisciplinary team the possibility of ICI rechallenge in each patient after stress cardiomyopathy, provided that close cardiac monitoring is ensured.

Physical examination on admission revealed bilateral pulmonary crackles. Initial laboratory testing showed leukocytosis with neutrophilia and high levels of C-reactive protein (198 mg/L). A chest computed tomography scan was performed, and it showed enlargement of mediastinal lymphadenopathy, ground-glass opacities, and pleural effusion. The result of a SARS-CoV-2 test was negative, the patient was admitted with a diagnosis of immunotherapy-induced pneumonitis, and corticosteroid treatment was started. A limited, point-of-care echocardiogram showed a normal left ventricular systolic function. Results of blood cultures and serologic tests for atypical respiratory pathogens were negative.

Five days after admission, the patient developed orthopnea and edema. New laboratory tests confirmed an increase in high-sensitivity troponin I (hs-TnI) (peak value, 276.2 ng/L; normal value, <53.5 ng/mL) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) (12,751 pg/mL). An electrocardiogram (ECG)

From the [a]Department of Cardiology, La Paz University Hospital, Madrid, Spain; [b]Department of Oncology, La Paz University Hospital, Madrid, Spain; and the [c]Cardio-Oncology Unit, La Paz University Hospital, Madrid, Spain.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 1, 2023; revised manuscript received April 20, 2023, accepted April 20, 2023.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2023.101881

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CMR = cardiac magnetic resonance

ECG = electrocardiogram

GLS = global longitudinal strain

hs-TnI = high-sensitivity troponin I

ICI = immune checkpoint inhibitor

irAE = immune-related adverse event

LGE = late gadolinium enhancement

NT-proBNP = N-terminal pro-B-type natriuretic peptide

showed sinus rhythm with negative T waves in the precordial leads (**Figure 1**). A new transthoracic echocardiogram was performed, and it showed mildly reduced left ventricular ejection fraction (51.6%, by Simpson's biplane method) with apical akinesia, reduced left ventricular global longitudinal strain (GLS) (−7.4%), base to apex circular gradient of strain (Video 1), and second-degree diastolic dysfunction (E/A 0.76), with reduced septal e′ (5 cm/s) and increased E/e′ (12.6).

PAST MEDICAL HISTORY

His medical history included hypertension, former smoking, dyslipidemia, and stage 4 chronic kidney disease, as well as colon adenocarcinoma treated with an adjuvant XELOX (capecitabine in combination with oxaliplatin) chemotherapy regimen 7 years earlier.

DIFFERENTIAL DIAGNOSIS

Although the patient denied chest pain, given his multiple cardiovascular risk factors, troponin elevation, and ECG changes, non-ST-segment elevation acute coronary syndrome (ACS) ranked first on the list of differential diagnoses. Once obstructive coronary artery disease was ruled out, immune checkpoint inhibitor (ICI)-related myocarditis and stress cardiomyopathy had to be considered. Other diagnoses, such as pericarditis or electrolyte disturbances, were considered less likely.

INVESTIGATIONS

Coronary angiography showed normal coronary arteries (Video 2). Given the history of atezolizumab treatment and the concomitant diagnosis of immune-related pneumonitis, cardiac magnetic resonance (CMR) was requested. CMR showed a nondilated left ventricle (end-diastolic volume, 43 mL/m^2; end-systolic volume, 17 mL/m^2) with a normal ejection fraction (59%) and stroke volume (47 mL), and a nondilated right ventricle (end-diastolic and end-systolic volumes, 46 and 21 mL/m^2, respectively) with a normal right ventricular ejection fraction (54%). CMR also confirmed improvement of apical akinesia and revealed normal native T_1 and T_2 values at the level of the midseptum and basal septum (1,173 and 37 ms, respectively) but a marked increase in the native T_1 and T_2 values in the apical segments (1,419 and 50 ms, respectively), which confirmed extensive apical edema (**Figures 2A and 2B**). These findings suggested stress cardiomyopathy. Late gadolinium enhancement (LGE) was not performed because of the patient's advanced chronic kidney disease, and given the previously mentioned findings, it was not deemed necessary at that point to make a definitive diagnosis.

FIGURE 1 Electrocardiogram Showing Sinus Rhythm With Negative T Waves in Precordial Leads

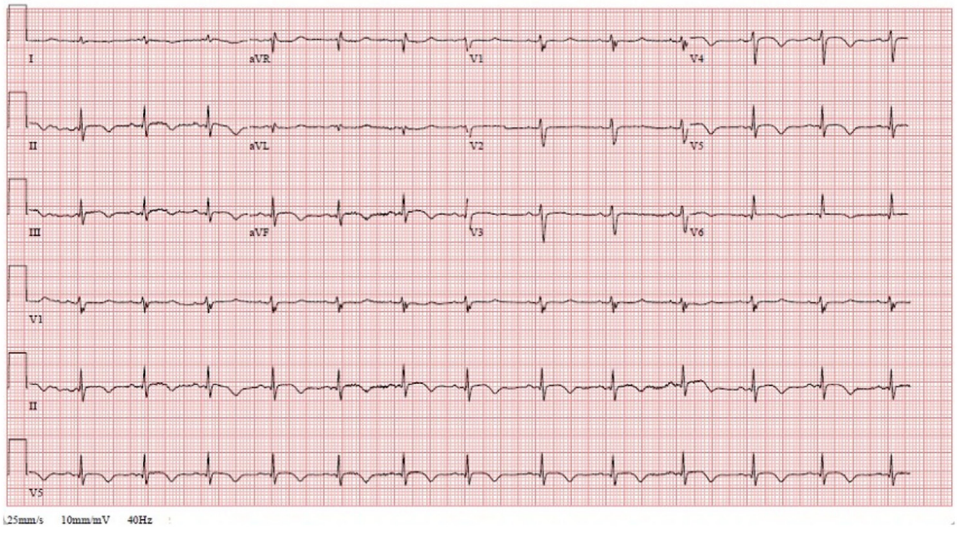
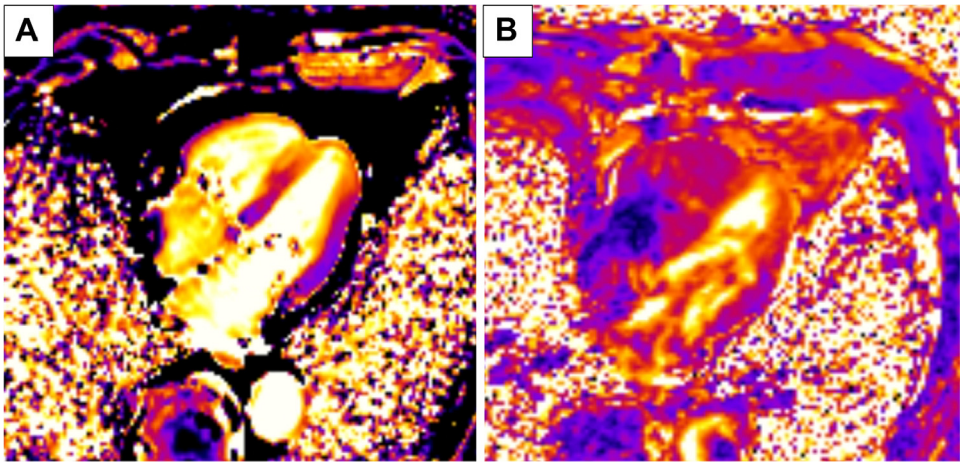


FIGURE 2 **Cardiac Magnetic Resonance T_1 and T_2 Mapping**



(A) Cardiac magnetic resonance T_1 mapping showed normal native T_1 values at the level of the midseptum and basal septum (1,173 ms), with a marked increase in the native T_1 values in the apical septum (1,419 ms). **(B)** Normal native T_2 values in the midseptum and basal septum (37 ms), but increased native T_2 values in the apical septum (50 ms). These findings are consistent with apical edema.

MANAGEMENT

Heart failure treatment, including β-blockers, angiotensin-converting enzyme inhibitors, and dapagliflozin, was initiated, as well as gradual corticosteroid tapering. The patient evolved favorably from the cardiologic and respiratory points of view. At discharge, laboratory tests showed normal hs-TnI levels and a significant decrease in NT-proBNP (915 pg/mL). A transthoracic echocardiogram showed normal left ventricular function and resolution of apical akinesia. Atezolizumab was temporarily discontinued.

DISCUSSION

ICIs have shown important benefits in the treatment of many malignant diseases. Despite the demonstrated clinical efficacy of these agents, activation of the immune system by immunotherapies can cause immune-related adverse events (irAEs). IrAEs can involve any system, and most irAEs resolve successfully with immunosuppression and cessation of ICI treatment. Immune-related cardiovascular toxicity, although less common, can be associated with high morbidity and mortality rates. The most frequently reported clinical manifestation is myocarditis; however, other manifestations, such as arrhythmia, ACS, or stress-induced cardiomyopathy, have been reported and should be taken into account when considering the differential diagnosis.[1]

Stress cardiomyopathy or takotsubo cardiomyopathy is a relatively rare and reversible form of cardiomyopathy. The clinical presentation mimics that of acute myocardial infarction. The diagnosis is suspected in the absence of obstructive coronary artery disease and can be confirmed by the demonstration of a regional left ventricular wall motion abnormality that is reversible.[2] Emotional or physical stressors are often present, although not always. The Task Force on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology proposes the following diagnostic criteria: transient regional wall motion abnormalities of right or left ventricular myocardium (preceded or not by a stressful trigger) that extend beyond a single epicardial vessel distribution, absence of culprit atherosclerotic coronary artery disease, new and reversible ECG abnormalities during the acute phase, relatively small elevation in cardiac troponin, and recovery of ventricular systolic function on cardiac imaging at follow-up.[3]

Takotsubo syndrome has been described in patients with cancer who were treated with ICIs, with an estimated incidence of 0.03%.[4] In a review of the World Health Organization global database of safety reports, 13 cases of stress cardiomyopathy were identified among patients treated with ICIs.[4] However, few cases of stress cardiomyopathy triggered by

TABLE 1 Recent Reported Cases of Stress Cardiomyopathy

First Author	ICI Therapy	Echocardiogram on Admission	CMR	Treatment	Echocardiogram During Follow-Up	ICI Rechallenge
Ederhy et al[7]	Nivolumab/ipilimumab	LVEF, 40% Apical akinesis	No LGE Normal T_2-mapping value	Methylprednisolone, 1 g/d	LVEF, 50% Resolution of apical akinesis	Not specified
Ederhy et al[7]	Nivolumab	LVEF, 40% GLS, −8.7% Medial and basal segments' akinesis	Increased T_2-mapping value	Methylprednisolone, 1 g/d ACE inhibitors and beta-blockers	LVEF, 60% GLS, −15% Resolution of apical akinesis	Not specified
Oldfield et al[8]	Nivolumab/ipilimumab	LVEF, 50% Apical akinesis	No LGE	Not specified	LVEF, 66% Resolution of apical akinesis	Recurrent cardiac adverse events
Tan et al[9]	Nivolumab	LVEF, 18% Medial and apical akinesis	LGE consistent with concomitant myopericarditis	Methylprednisolone, 1 mg/kg every 12 h	LVEF, 56% Resolution of apical akinesis	No further cancer therapy pursued
Serzan et al[10]	Nivolumab/ipilimumab	Apical akinesis	Increased T_2 and T_1-mapping values Diffuse LGE	Beta-blockers	LVEF, 65% Resolution of apical akinesis	Not specified

ACE = angiotensin-converting enzyme; CMR = cardiac magnetic resonance; GLS = global longitudinal strain; ICI = immune checkpoint inhibitor; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction.

ICIs have been reported in the absence of other stressful clinical situations or simultaneous cardiotoxic treatments.[5,6] Recent cases of stress cardiomyopathy reported in the literature are summarized in **Table 1**.[7-10]

Whether stress cardiomyopathy results from direct or indirect toxicity of ICIs is unknown. It has also been suggested that this condition may result from late toxicity from previous cycles of chemotherapy. Research is needed to determine the mechanisms that lead to this presentation.[11,12]

The differential diagnosis should include ACS and myocarditis, given the implications for management and prognosis. Endomyocardial biopsy has traditionally played a key role in the differential diagnosis,[10] although the routine use of this procedure is limited by its invasive nature and the need for expertise in both performance and interpretation. Early cardiac imaging is essential in the noninvasive diagnosis of cardiovascular toxicity. CMR allows for detailed anatomical visualization and accurate functional assessment, and T_1 and T_2 myocardial mapping and LGE provide detailed tissue characterization that offers the potential for definitive diagnosis without invasive testing.[13] The typical findings in takotsubo syndrome include high T_1 and T_2 signal intensity (edema) and no LGE (when present, LGE is diffuse and low density, and it usually resolves at follow-up). In myocarditis, high T_2 signal intensity (edema) and LGE with a nonischemic distribution (often epicardial) are the typical findings.[3] We did not perform gadolinium contrast-enhanced sequences because of the patient's stage 4 chronic kidney disease. In our patient, CMR findings were consistent with stress cardiomyopathy. The suspected diagnosis was established, considering the finding of regional wall motion abnormalities extending beyond a single epicardial vessel distribution and the demonstration of myocardial edema in a takotsubo pattern, absence of coronary artery stenosis, ECG abnormalities, and high NT-proBNP levels with a paradoxical low hs-TnI peak, with no further endomyocardial biopsy needed. Echocardiography and ECG in follow-up visits confirmed the reversibility of regional wall motion abnormalities and negative T waves, thus confirming the diagnosis of takotsubo syndrome.

In patients with cancer, the 2022 European Society of Cardiology guidelines on cardio-oncology recommend coronary angiography and CMR to exclude ACS and myocarditis, respectively, for the diagnosis of takotsubo syndrome.[14] Of note, the guidelines highlight the importance of early cardiac imaging, given the transient nature of left ventricular involvement.[14]

Treatment of stress cardiomyopathy is mainly supportive, including stressor control. Interruption of the culprit chemotherapy agent is recommended.[14] In ICI-associated takotsubo syndrome, the role of immunosuppression is unknown; however, if CMR shows myocardial inflammation in a takotsubo pattern, guidelines recommend administering intravenous methylprednisolone,[14] given the high overlap between myocarditis and takotsubo and the high morbidity and mortality of the former. Although most often cardiomyopathy resolves with a mild clinical course in a high percentage of cases, the in-hospital mortality rate is 2% to 5%; death is mainly caused by refractory cardiogenic shock or ventricular fibrillation.[3] In our case, early initiation of corticosteroid agents could explain the rapid resolution and the mild clinical course, although the evidence is scarce.

The decision to rechallenge patients with similar agents after recovery should be individualized because the evidence is limited. If rechallenge is chosen, close cardiac monitoring is recommended.[14]

Our case is exceptional because stress cardiomyopathy secondary to ICIs is a rare entity and an unusual cause of heart failure in patients undergoing cancer treatment. Diagnostic suspicion along with early cardiac imaging and prompt immunosuppressive treatment allowed avoiding more invasive diagnostic methods (eg, cardiac biopsy, which is excessively aggressive in cancer patients and has a high risk of procedure-related complications), thus preventing progression of the disease and aiding earlier and more complete recovery.

FOLLOW-UP

A new transthoracic echocardiogram was performed 1 month after discharge. It showed a normal left ventricular ejection fraction (57.9%), normal GLS (−21%), and no regional wall motion abnormalities (Video 3). The ECG during this visit was normal.

Considering the final diagnosis of stress cardiomyopathy, the patient's preferences, and the normalization of cardiac function, the multidisciplinary team decided to continue atezolizumab, with regular cardiac biomarker monitoring and close cardiology follow-up. No new cardiovascular events of interest have occurred 6 months after discharge.

CONCLUSIONS

ICIs have led to improved prognosis in several cancers, but cardiovascular irAEs can be serious. In patients at risk of cardiotoxicity, close cardiac monitoring is recommended. When cardiotoxicity is suspected, early cardiac imaging is often helpful in diagnosis and allows early initiation of treatment.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Lucía Cobarro, Department of Cardiology, La Paz University Hospital, Paseo de la Castellana, 261, Madrid 28046, Spain. E-mail: luciacobarro@hotmail.com. Twitter: @luciacobi.

REFERENCES

1. Patel RP, Parikh R, Gunturu KS, et al. Cardiotoxicity of immune checkpoint inhibitors. *Curr Oncol Rep*. 2021;23(7):79.

2. De Chazal HM, Del Buono MG, Keyser-Marcus L, et al. Stress cardiomyopathy diagnosis and treatment: JACC state-of-the-art review. *J Am Coll Cardiol*. 2018;72(16):1955-1971.

3. Lyon AR, Bossone E, Schneider B, et al. Current state of knowledge on takotsubo syndrome: a position statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2016;18(1):8-27.

4. Ederhy S, Dolladille C, Thuny F, Alexandre J, Cohen A. Takotsubo syndrome in patients with cancer treated with immune checkpoint inhibitors: a new adverse cardiac complication. *Eur J Heart Fail*. 2019;21(7):945-947.

5. Singhal S, Patel G, Singh RB, Goyal A, Avgush K, Koka J. Atezolizumab-induced autoimmune diabetes mellitus presenting as diabetic ketoacidosis and takotsubo cardiomyopathy. *BMJ Case Rep*. 2022;15(7):e250662.

6. Airò G, Maffezzoli M, Lazzarin A, et al. Takotsubo syndrome in a patient with metastatic renal cell carcinoma treated with pembrolizumab plus axitinib. *Immunotherapy*. 2022;14(16):1297-1305.

7. Ederhy S, Cautela J, Ancedy Y, Escudier M, Thuny F, Cohen A. Takotsubo-like syndrome in cancer patients treated with immune checkpoint inhibitors. *J Am Coll Cardiol Img*. 2018;11(8):1187-1190.

8. Oldfield K, Jayasinghe R, Niranjan S, Chadha S. Immune checkpoint inhibitor-induced takotsubo syndrome and diabetic ketoacidosis: rare reactions. *BMJ Case Rep*. 2021;14(2):e237217.

9. Tan NYL, Anavekar NS, Wiley BM. Concomitant myopericarditis and takotsubo syndrome following immune checkpoint inhibitor therapy. *BMJ Case Rep*. 2020;13(9):e235265.

10. Serzan M, Rapisuwon S, Krishnan J, Chang IC, Barac A. Takotsubo cardiomyopathy associated with checkpoint inhibitor therapy. *J Am Coll Cardiol CardioOnc*. 2021;3(2):330-334.

11. Shalata W, Abu-salman A, Steckbeck R, Mathew Jacob B, Massalha I, Yakobson A. Cardiac toxicity associated with immune checkpoint inhibitors: a systematic review. *Cancers (Basel)*. 2021;13(20):5218.

12. Lyon AR, Yousaf N, Battisti NML, Moslehi J, Larkin J. Immune checkpoint inhibitors and cardiovascular toxicity. *Lancet Oncol*. 2018;19(9):e447-e458.

13. Friedrich MG, Sechtem U, Schulz-Menger J, et al. Cardiovascular magnetic resonance in myocarditis: a JACC white paper. *J Am Coll Cardiol*. 2009;53(17):1475-1487.

14. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43(41):4229-4361.

KEY WORDS cardio-oncology, cardiotoxicity, immune checkpoint inhibitors, stress cardiomyopathy

APPENDIX For supplemental videos, please see the online version of this article.