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CASE REPORT

INTERMEDIATE

CLINICAL CASE

Immune Checkpoint Inhibitor-Associated Myocarditis

A Run of Bad Luck or Rather Deficient-Monitoring Protocol?

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ABSTRACT

Immune checkpoint inhibitors (ICIs) can induce immunity-related adverse events. We demonstrate the clinical use of cardiac magnetic resonance and endomyocardial biopsy in the diagnosis and subsequent monitoring of ICI-associated myocarditis, suggesting the need to establish and evaluate a cardiac monitoring protocol for patients under ICI therapy. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:630–5) © 2020 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/).

Immunotherapy with immune checkpoint inhibitors (ICIs) revolutionized the therapy of solid tumors such as lung cancer. Novel compounds addressing targets like programmed death (PD)-1 receptor or programmed death-ligand 1 (PD-L1) have been shown to improve overall survival in advanced, metastatic non-small cell lung cancer (NSCLC). Today, nivolumab, pembrolizumab, and atezolizumab are clinically approved antibodies (targeting PD-1 or PD-L1) in lung cancer treatment. In this context, pembrolizumab is an ICI that is currently recommended as the standard-of-care first-line treatment in advanced NSCLC—either as monotherapy or in combination with platinum-based chemotherapy (independent of PD-L1 expression) (1).

LEARNING OBJECTIVES

- To identify early signs of an immune checkpoint inhibitor–associated myocarditis, assess arrhythmic risk, and opt for the right treatment.
- To be aware of the utility of cardiac magnetic resonance in the diagnosis of immune checkpoint inhibitor–associated myocarditis.

Mechanistically, immune checkpoints are responsible for preventing the immune system from attacking the body's own tissue, and many tumors exploit these inhibitory pathways (e.g., the PD-1/PD-L1/2 pathway) as a mechanism of immune resistance (2). Therefore, on the one hand, blockade of immune checkpoints can enhance antitumor immunity and reinvigorate a patient's immune system to fight cancer; however, on the other hand, blockade of immune checkpoints also induces a broad spectrum of immune-related adverse events (irAEs) owing to aberrant activity of autoreactive immune cells. Unfortunately, any organ system can be affected by irAEs, yet the gastrointestinal

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tract, endocrine glands, skin, and liver are most commonly impacted.

So far, the cardiovascular system was believed to be among the least affected organs by immunotoxicity with the incidence of ICI-associated myocarditis ranging from 0.06% to 1% (3). However, underestimation is expected due to lack of awareness, and the real incidence rates are therefore expected to be higher. Taking ICI-related cardiotoxicity into consideration for the further clinical course and outcome of the underlying disease, increased alertness and close cardiac monitoring are crucial for early identification and treatment. Here, we present the case of a young patient with metastatic NSCLC who developed severe congestive heart failure with cardiogenic shock and recurrent ventricular tachycardia owing to autoimmune myocarditis following treatment with pembrolizumab.

HISTORY OF PRESENTATION

A 30-year-old woman with a history of metastatic NSCLC presented to the emergency department of a local general hospital with sudden onset of severe shortness of breath. In the days before, the patient had noticed decreased exercise capacity that was initially attributed to her underlying disease. Physical examination revealed an afebrile, generally ill appearing, but alert and oriented young adult. She had tachycardia, S_1/S_2 were normal without any murmur, gallop, or rub. Blood pressure was low (90/70 mm Hg) and her respiration rate was high (25/min). Lung auscultation revealed bilateral crepitant moist rales without wheezing and diminished breath sounds over the lung bases. Her abdomen was soft, nontender, and nondistended. Pitting edema was prominent in her feet and ankles. There were no skin lesions or rash apparent.

PAST MEDICAL HISTORY

Six months before the present admission, the patient was diagnosed with pulmonary adenocarcinoma of the left upper lobe with mediastinal lymph node and multiple liver metastases. Excessive tiredness and fatigue were her major complaints. Palliative systemic chemotherapy was immediately initiated with 2 cycles of cisplatin and vinorelbine followed by 2 cycles of carboplatin, pemetrexed, and pembrolizumab after consideration of the high PD-L1 tumor proportion score of 95% and further exclusion of molecular targetable lesions. Subsequent response assessment according to RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 guidelines revealed partial remission. Owing to considerable nausea and vomiting, chemotherapy was switched to pembrolizumab monotherapy that was well tolerated by the patient at the beginning. Unfortunately, dyspnea and signs of acute heart failure suddenly developed following 6 cycles of pembrolizumab.

DIFFERENTIAL DIAGNOSIS

The initial differential diagnoses comprised viral myocarditis, immune-related myocarditis following ICI therapy, malignant pericarditis, and pulmonary embolism. After exclusion of pulmonary embolism via computed tomography, absence of a relevant pericardial effusion and echocardiographic confirmation of a left ventricular (LV) dilatation with severe systolic dysfunction, myocarditis appeared to be the most likely diagnosis.

INVESTIGATIONS

On present admission, resting electrocardiogram (ECG) demonstrated a sinus tachycardia with a rate of 110/min and T-wave inversion in leads I and aVL. Laboratory studies revealed no signs of inflammation: C-reactive protein was 0.24 mg/dl (reference range [RR] <0.5 mg/dl), total white blood cell count was $8.24 \times 10^3/\mu l$ (RR = 3.5 to $9.8 \times 10^3/\mu l$), and there were no signs of bleeding (hemoglobin = 13.3 g/dl; RR <12 g/dl). Pronounced elevated N-terminal pro-B-type natriuretic peptide (18,147 pg/ml; RR <115 pg/ml) and high-sensitivity troponin T (205 ng/l; RR <14 ng/l) indicated severe heart failure with myocardial injury. Transthoracic echocardiography showed a dilated LV (LV end-diastolic diameter = 55 mm) with severely reduced systolic function owing to global hypokinesis (LV ejection fraction [LVEF] = 18%), and thoracic ultrasound showed large bilateral pleural effusion.

In order to identify the underlying cause of this severe cardiac disease, a cardiac magnetic resonance (CMR) study (**Figure 1**, Videos 1 and 2) was performed on a Philips 1.5-T scanner (Ingenia, Philips Healthcare, Best, the Netherlands). CMR confirmed the aforementioned LV dilatation (LV end-diastolic volume index = 125 ml/m^2) and reduced systolic function (LVEF = 32%). In addition, presence of subendocardial to intramural late gadolinium enhancement (LGE) with concomitant myocardial edema was documented in the basal inferoseptal LV wall—a pattern quite different from the characteristic one of "viral" myocarditis that is typically localized in the subepicardial regions of the LV inferolateral wall and less frequently in anteroseptal segments.

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

ICI = immune checkpoint inhibitor

irAE = immune-related adverse event

LGE = late gadolinium enhancement

LV = left ventricular

LVEF = left ventricular ejection fraction

MMF = mycophenolate mofetil

NSCLC = non-small cell lung cancer

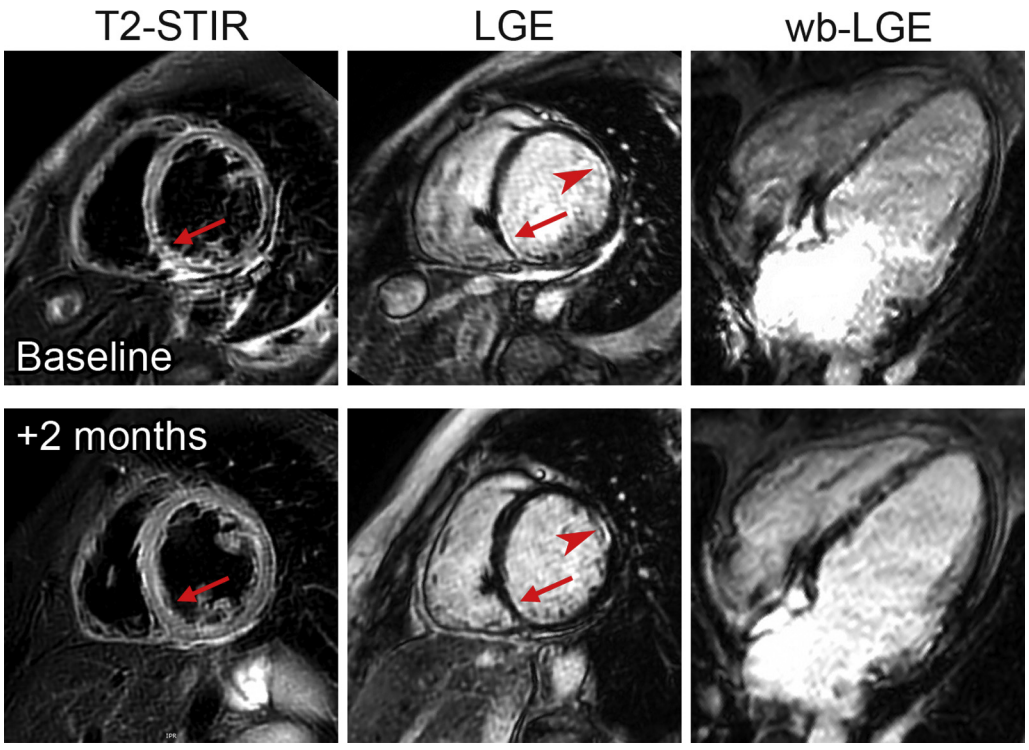
PD = programmed death

PD-L = programmed death-ligand

RR = reference range

VT = ventricular tachycardia

FIGURE 1 Cardiac Magnetic Resonance Images



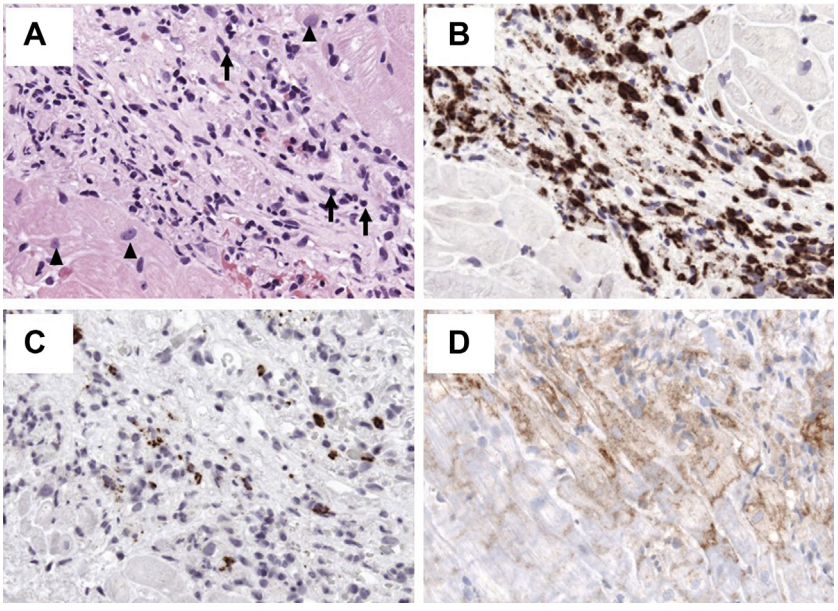
T2-weighted short tau inversion recovery (T2-STIR) **(first column)** and late gadolinium enhancement (LGE) **(second and third columns)** cardiac magnetic resonance images in the acute phase **(top row)** and 2 months later **(bottom row)** in a midventricular short-axis view and a 4-chamber view. A pronounced edema in the basal inferoseptal wall **(arrow)** on T2-STIR images with corresponding LGE in the subendocardial myocardial layers of the basal inferoseptal **(arrow)** and of the basal anterolateral wall **(arrowhead)** was present at initial examination **(top row)**. A marked regression of the aforementioned findings was seen 2 months later **(bottom row)**. A wideband (wb) inversion pulse reduced hyperintensity artifacts originating from the implantable cardioverter-defibrillator and allowed complete assessment of the myocardium also in the 4-chamber view **(third column)**.

For further cardiac work-up, coronary angiography was performed showing normal coronary arteries, followed by LV endomyocardial biopsy taken from the aforementioned LGE-positive areas identified by the preceding CMR. The histopathological and immunohistochemical examinations revealed an acute lymphocytic myocarditis with $CD3^{+}$-T cell and $CD20^{+}$-B cell infiltrates and extensive myocyte necrosis (Figures 2A and 2B). Furthermore, polymerase chain reaction assays were positive for low levels of DNA from parvovirus B19 and human herpesvirus 6. Nevertheless, the diagnosis of a predominant ICI-associated autoimmune myocarditis was favored due to: 1) substantial myocardial infiltration of $CD20^{+}$-B lymphocytes that is not typically seen to such an extent in case of viral myocarditis (Figure 2C); and 2) the pattern of myocardial damage documented by CMR. In addition, immunohistochemical staining revealed high expression of myocardial PD-L1, consistent with prior studies suggesting a cytokine-induced cardioprotective mechanism (Figure 2D).

MANAGEMENT

Owing to initial cardiogenic shock, the patient was admitted to the intensive care unit and treated with inotropic (dobutamine) and vasopressor (epinephrine) agents. Ultrasound-guided thoracentesis on both sides and diuretics (furosemide, spironolactone) achieved decongestion. ECG monitoring showed excessive ventricular ectopic activity that subsequently resulted in symptomatic ventricular tachycardia (VT). Despite initiation of high doses of antiarrhythmic drugs (amiodarone, lidocaine) and successive substitution of magnesium, recurrence of additional VT episodes could not be

FIGURE 2 Histopathological Assessment of Myocardial Tissue Obtained From Endomyocardial Biopsy



(A) Histology revealed extensive myocyte necrosis in association with mainly focal immune cell infiltrates (hematoxylin and eosin staining). Immunohistology detects **(B)** numerous CD3-positive T cells and **(C)** a significant amount of B cells. **(D)** Expression of programmed death-ligand 1 is found on myocytes within areas of inflammation.

avoided. In order to suppress premature ectopic beats and prevent recurrent VT, we decided to perform ventricular overdrive pacing. This was accomplished with the placement of a temporary transvenous pacemaker programmed at 90 beats/min (heart rate before pacing was 60 to 70 beats/min). Owing to suspected ICI-associated myocarditis with acute heart failure, intensified immunosuppressive therapy with 1,000 mg methylprednisolone daily for 3 days was initiated immediately. After hemodynamic stabilization, the temporary transvenous pacemaker was immediately replaced by a magnetic resonance-conditional implantable cardioverter-defibrillator as the patient was considered to be in high arrhythmic risk. After histological confirmation of ICI-associated myocarditis, the patient was continued on high-dose prednisolone (100 mg daily) and mycophenolate mofetil (MMF) (1,000 mg twice a day), a treatment based on current international guidelines (4). The patient received standard heart failure medication and was discharged with an angiotensin II receptor blocker, β-blocker, and diuretics. After implementation of this therapy, no further VT episodes were documented and no device therapy has occurred so far.

DISCUSSION

To the best of our knowledge, this is the first case demonstrating the full spectrum of ICI-associated myocarditis, with a complete diagnostic work-up comprising not only ECG and echocardiography, but also noninvasive CMR, invasive LV endomyocardial biopsy, and subsequent therapeutic interventions to treat heart failure and life-threatening arrhythmias. ICIs such as pembrolizumab are well known to induce a broad spectrum of irAEs owing to activation of autoimmune mechanisms; however, cardiotoxicity constitutes an underestimated, significant irAE and warrants further clinical alertness and investigation.

More than half of all reported cases of ICI-associated myocarditis occurred rather early in the course of treatment (5). Based on this limited evidence of rapid onset shortly after initiation of ICI therapy, a pathophysiological mechanism based on the augmentation of pre-existing memory T cell response was suggested (6). However, the late onset of heart failure seen in some cases cannot completely be explained by this hypothesis. One may assume that in those cases with rather mild myocarditis, the little (if at all) decline in LV systolic

function is initially well tolerated and, unfortunately, not diagnosed in time owing to lack of (appropriate) cardiac monitoring. In this context, other cardiac mechanisms that predominantly result in rather subendocardial damage of the myocardium seem to occur—following the initial T-cell-driven phase.

Importantly, in the present case, the patient suffered from clinically new onset severe heart failure with cardiogenic shock after 6 cycles of pembrolizumab. We do not believe that such an advanced form of autoimmune cardiotoxicity just occurred shortly before her admission and rather expect that some degree of autoimmune myocarditis was ongoing already in the weeks before—but was not detected due to: 1) missing clinical symptoms at that stage; and 2) suboptimal cardiac monitoring. It is noteworthy that the pattern of LGE documented by CMR was not typical for "viral" myocarditis and rather was suggestive of an ischemia-driven lesion, as the subendocardium was predominantly affected. However, obstructive CAD was ruled out in this patient, and such subendocardial patterns of myocardial damage (in the absence of obstructive CAD) were already described in other autoimmune diseases with cardiac involvement such as Churg-Strauss syndrome, systemic lupus erythematosus, or other forms of vasculitis (7,8). Possible causes for such a subendocardial damage are: 1) the occurrence of coronary vasospasm or microvascular dysfunction in case of myocardial inflammation (9,10); and 2) increased LV volume and pressure load in cases of impaired systolic function with subsequent damage in the coronary capillary network that is located in the subendocardium. Hence, we advocate the constitution of a consensus panel addressing this issue. The experienced members of such a panel should make the recommendations regarding the appropriate extent, modality, and timing of monitoring and surveillance of patients undergoing treatment with ICIs, as well as recommendations regarding appropriate initial emergent or mitigating therapy and considerations for alternate oncologic initiatives. In our opinion, cardiac examinations should comprise at least resting ECG, cardiac enzymes, and transthoracic echocardiography—followed by additional CMR ± invasive work-up in case of abnormal cardiac findings.

FOLLOW-UP

Two months after the first CMR scan, a follow-up CMR study was performed (**Figure 1**, Videos 3 and 4) using the same CMR protocol. At this time, LV systolic function was markedly improved (LVEF = 48%) and myocardial edema had completely resolved. However, the aforementioned LGE pattern was still evident, suggesting a permanent damage (fibrotic scar) of the myocardium. Moreover, the patient reported a significant improvement in her exercise capacity with only slight limitation during ordinary activity (New York Heart Association functional class II) and complete remission of peripheral edema. Although immunosuppressive therapy with MMF was continued, prednisolone was gradually reduced after discharge from hospital. Additional assessment of tumor burden 4 months after the last oncological therapy did not show any relevant progression of her lung disease.

CONCLUSIONS

This case gives an in-depth insight into the clinical course of ICI-associated myocarditis, proposes a different pathophysiological background, and underlines the importance of establishing routine and close cardio-oncological management strategies in order to detect potential cardiac irAEs timely. Furthermore, this case highlights the necessity for appropriate monitoring guidelines regarding the growing number of patients undergoing ICI therapy. A multidisciplinary team approach composed of primary care providers, oncologists, cardiologists, and specialized cardiopathologists is required in order to optimize diagnostic and therapeutic algorithms as well as to prevent patients from severe ICI-related cardiotoxicity.

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REFERENCES

1. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:iv192–237.

2. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252–64.

3. Ganatra S, Neilan TG. Immune checkpoint inhibitor-associated myocarditis. Oncologist 2018;23:879–86.

4. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36:1714–68.

5. Atallah-Yunes SA, Kadado AJ, Kaufman GP, Hernandez-Montfort J. Immune checkpoint inhibitor therapy and myocarditis: a systematic review of reported cases. J Cancer Res Clin Oncol 2019;145:1527–57.

6. Martinez-Calle N, Rodriguez-Otero P, Villar S, et al. Anti-PD1 associated fulminant myocarditis after a single pembrolizumab dose: the role of occult pre-existing autoimmunity. Haematologica 2018;103:e318–21.

7. Baccouche H, Yilmaz A, Alscher D, Klingel K, Val-Bernal JF, Mahrholdt H. Images in cardiovascular medicine. Magnetic resonance assessment and therapy monitoring of cardiac involvement in Churg-Strauss syndrome. Circulation 2008;117:1745–9.

8. Bietenbeck M, Florian A, Shomanova Z, Klingel K, Yilmaz A. Novel CMR techniques enable detection of even mild autoimmune myocarditis in a patient with systemic lupus erythematosus. Clin Res Cardiol 2017;106:560–3.

9. Yilmaz A, Mahrholdt H, Athanasiadis A, et al. Coronary vasospasm as the underlying cause for chest pain in patients with PVB19 myocarditis. Heart 2008;94:1456–63.

10. Vallbracht KB, Schwimmbeck PL, Kuhl U, Rauch U, Seeberg B, Schultheiss HP. Differential aspects of endothelial function of the coronary microcirculation considering myocardial virus persistence, endothelial activation, and myocardial leukocyte infiltrates. Circulation 2005;111:1784–91.

KEY WORDS **CMR, irAE, myocarditis, pembrolizumab, ventricular tachycardia**

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