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CASE REPORT

Keeping immune checkpoint inhibitor myocarditis in check: advanced circulatory mechanical support as a bridge to recovery

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Abstract

Immune checkpoint inhibitor (ICI)-associated myocarditis is a rare, potentially life-threatening complication of immunotherapy. We report a case of a 60-year-old female with a history of colorectal cancer treated with nivolumab immunotherapy who presented with new cardiomyopathy complicated by cardiogenic shock and ventricular arrhythmias. Treatment of ICI-associated myocarditis requires aggressive immunosuppression and supportive therapy. In this case, the patient required advanced mechanical circulatory support as a bridge to recovery. This case highlights the complexity of diagnosis, haemodynamic management, and treatment of fulminant ICI myocarditis.

Keywords Cardiomyopathy; Cardiac assist device; Acute heart failure; Immune checkpoint inhibitor myocarditis; Cardiooncology

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Introduction

Immunotherapy has revolutionized cancer treatment by harnessing the native immune system for treatment of advanced malignancies. For immune regulation, T lymphocytes express receptors, including CTLA-4 and PD-1 receptors, which trigger coinhibitory signalling pathways to prevent T lymphocyte proliferation and migration. Tumour cells can express ligand receptors, like PD-L1, to initiate this pathway and down-regulate the local cellular immune response. Monoclonal antibodies, called immune checkpoint inhibitors (ICIs), block these receptors to reactivate the native antitumor response.[1–3] Since the first ICI was approved in 2011, seven approved agents are indicated for over 40 malignancies.[1] However, in 2014, the first series of cases of ICI-associated myocarditis were reported with a high rate of fatality, from 27% to 50%.[4,5] Multiorgan toxicities, including cardiovascular, are due to off-target activation of the immune response. Recognized cardiovascular immune-mediated toxicities include myocarditis, vasculitis, pericarditis, arrhythmias, and Takotsubo cardiomyopathy.[1,4] Although ICI-associated myocarditis is uncommon with an incidence of about 1%,[6] it is critical to recognize this potentially fatal complication.[7]

Case report

A 60-year-old female with a history of colon cancer and Graves' disease was sent to the emergency department from clinic for an abnormal electrocardiogram (ECG). She had been referred for 3 weeks of palpitations and markedly reduced exercise tolerance. She denied chest pain, syncope, orthopnoea, paroxysmal nocturnal dyspnoea, or lower extremity oedema. She reported a single use of cocaine 7 days earlier.

From an oncologic standpoint, the patient was diagnosed 9 months earlier with moderately differentiated T3N1 adenocarcinoma of the colon with a sporadic microsatellite instability mutation. She underwent hemicolectomy, three cycles of XELOX (capecitabine and oxaliplatin) chemotherapy and ongoing ICI therapy with nivolumab (first and last dose were 5 and 2 months prior).

Her examination was remarkable for sinus tachycardia to 115 bpm, and cool extremities without evidence of volume overload. Initial ECG (*Figure 1A,B*) demonstrated a bidirectional fascicular ventricular tachycardia and diffuse ST segment elevation. Laboratory testing revealed significantly elevated troponin, brain natriuretic peptide and liver enzymes (*Table 1*). Influenza B IgG and IgM serologies were positive. Echocardiography demonstrated a newly reduced left ventricular ejection fraction (LVEF) of 30% with global hypokinesis. Coronary angiography revealed no significant epicardial coronary artery disease. Cardiac magnetic resonance imaging demonstrated normal left ventricular size with globally reduced systolic function (LVEF 38%) without delayed myocardial enhancement. Her initial diagnosis was presumed influenza-associated myocarditis and unlikely ICI-related,

Figure 1 (A) Baseline normal electrocardiogram (ECG) prior to initiation of chemotherapy and immunotherapy. (B) Initial presenting ECG with alternating fascicular ventricular tachycardia with 1:1 V-A conduction and diffuse ST segment elevation. Ventricular morphologies correlate to outflow tract (left bundle branch morphology with superior axis) and apical (superior axis, negative precordial concordance) origins. (C) ECG on readmission to the emergency department unchanged from prior admission. (D) Repeat ECG prior to discharge showing normal sinus rhythm, normal QRS duration, new inferior Q waves, and poor R wave progression.

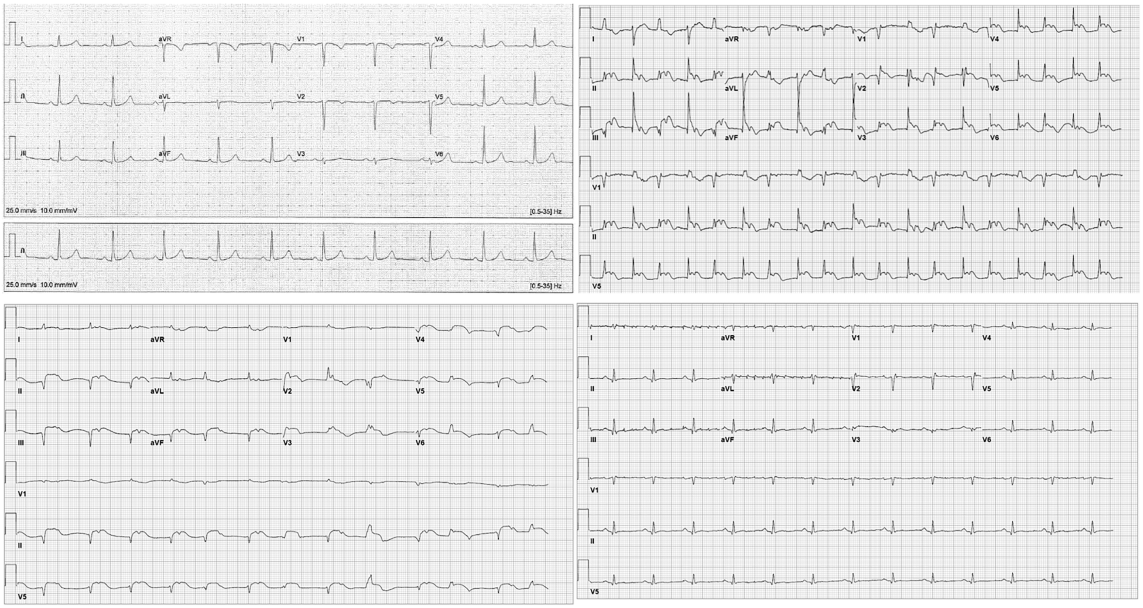


Table 1 Laboratory values throughout clinical course

Laboratory test (reference range)	Initial presentation	Readmission (HD 1)	ECMO cannulation (HD 3)	Discharge (HD 19)
BNP (<100 pg/mL)	173	1188	N/A	325
Troponin I (<0.1 ng/mL)	30.2	18.2	9.2	0.09
ALT (8–64 U/L)	361	374	205	42
AST (13–47 U/L)	688	431	338	24
Creatinine (0.6–1.3 mg/dL)	0.58	1.69	3.37	1.79
Potassium (3.6–5.3 mmol/L)	4.4	5.5	3.4	3.4
Lactate (5–25 mg/dL)	N/A	24	45	8

Laboratory values taken throughout both hospitalizations. During readmission, all laboratory values decreased with immunosuppressive treatment and hemodynamic support. Although there may have been an element of hepatic congestive secondary to heart failure, liver enzymes (ALT & AST) were primarily thought to be elevated due to ICI-associated hepatitis and similarly responded to immunosuppression.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, B-type natriuretic peptide; ECMO, extracorporeal membrane oxygenation; HD, hospital day; ICI, immune checkpoint inhibitor.

given the distant time from immunotherapy treatments and normal CMR. Metoprolol succinate, lisinopril, and spironolactone were initiated. Oral amiodarone was initiated for high-risk arrhythmia, and she was discharged on hospital day (HD) 5 with a LifeVest (Zoll Medical Corporation, Chelmsford, MA) wearable defibrillator.

Nine days after discharge, she returned to the emergency department with worsening weakness and nausea. Her vitals were significant for tachycardia and hypotension. Exam revealed diminished distal pulses and cool extremities. Laboratory testing demonstrated worsening abnormalities from her prior admission (*Table 1*). ECG was unchanged (*Figure 1C*). Her presenting blood pressure was 60/40 mmHg with altered mental status. Bedside echocardiogram demonstrated LVEF $<$ 10% and an intravenous dopamine infusion (2 mcg/kg/min) was initiated. Shortly thereafter, she experienced sustained ventricular tachycardia at 160 bpm with palpable pulses. Given concern for worsening cardiogenic shock, she was emergently transported to the cardiac catheterization laboratory for right heart catheterization and consideration of mechanical circulatory support.

Right heart catheterization demonstrated a severely depressed cardiac index with mildly elevated right-sided filling pressures (*Table 2*). A multidisciplinary discussion between oncology and cardiology highlighted the heterogeneity of onset, lack of CMR sensitivity in early disease, and importance of prompt treatment for ICI-associated myocarditis. Immunosuppression was empirically started with high-dose corticosteroids, antithymocyte globulin, and later plasmapheresis (*Figure 2B*). An endomyocardial biopsy (EMB) confirmed ICI-associated myocarditis (*Figure 2A*). An Impella CP (Abiomed, Danvers, MA) was inserted for haemodynamic support. Nitroprusside and milrinone were added for vasodilator and inotropic support; however, the patient developed right heart failure (*Table 2*) and hypotension refractory to multiple vasopressors. Haemodynamic support was escalated to veno-arterial extracorporeal membrane oxygenation (VA-ECMO). Notably, she was diagnosed with ICI-associated ocular myasthenia, colitis, and hepatitis.

With continued immunosuppression, haemodynamics and laboratory markers gradually improved (*Figure 2B*). Her Impella was removed on HD 7, and ECMO was decannulated on HD 8. Repeat CMR revealed new patchy mid myocardial delayed enhancement consistent with myocarditis (*Figure 2C*). Echocardiogram showed improved LVEF of 40%. She was discharged on a steroid taper with serial echocardiograms and serum troponins. ICI therapy was never reinitiated. At 2 years of follow up, she remains clinically stable with New York Heart Association Class II symptoms, LVEF mildly declined to 35% on medical therapy, and an implantable cardioverter defibrillator was placed for primary prevention. She currently has no evidence of recurrent malignancy or myocarditis.

Discussion

This case demonstrates the complexity of diagnosis and management of ICI-associated myocarditis, an uncommon but potentially fatal complication. Clinical presentation varies from isolated biomarker abnormalities to heart failure, arrhythmia, and cardiogenic shock. Although 81% of cases occur within 3 months of initiating therapy, onset ranges from days to over 1 year indicating the importance of maintaining a high index

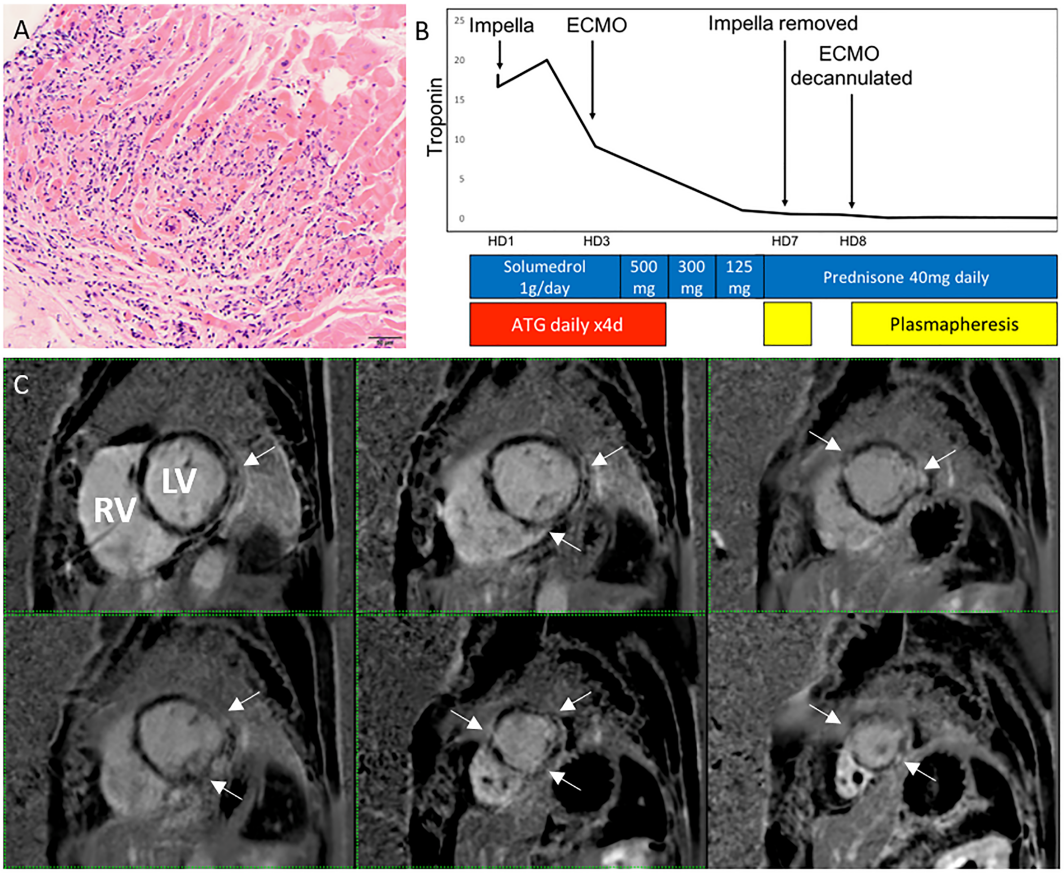
Table 2 Serial right heart catheterization (RHC) data

Variable	Pre-Impella implantation (HD 1)	Post-Impella implantation (HD 1)	Impella, inotropes, vasodilators (HD 2)	Pre-ECMO cannulation (HD 3)	Impella removal (HD 7)	Pre-ECMO decannulation (HD 8)	Post-ECMO decannulation (HD 9)
RAP (mmHg)	11	16	9	21	9	4	1
PAP (mmHg)	24/16 (18)	24/16 (18)	19/10 (14)	14/10 (12)	20/12 (15)	17/9 (12)	14/5 (8)
PCWP (mmHg)	10	18	N/A	N/A	NA	NA	NA
Cardiac output (L/min) TD (Fick)	1.30 (2.5)	2.4 (3.6)	3.9	2.7	4.0	4.6	3.6
Cardiac index (L/min/m^2) TD (Fick)	0.74 (1.46)	1.36 (2.0)	2.23	1.54	2.29	2.628	2.05

(I) Prior to Impella CP placement, RHC shows mildly elevated right-sided filling pressures with severely reduced cardiac output, which in conjunction with evidence of end organ damage indicated cardiogenic shock. (II) Post-Impella CP implantation, there is improvement of cardiac output, but increased left and right-sided filling pressures. (III) On Impella CP support (P8, flow rate 3.5 L/min) with inotropic support on milrinone (maximum dose 0.4 mcg/kg/min) and vasodilator therapy on nitroprusside (maximum dose 2 mcg/kg/min), haemodynamics improved significantly with normalization of left-sided and right-sided filling pressures and improvement of cardiac index $>$ 2.2 L/min/m^2. (IV) Patient then had haemodynamic decompensation with hypotension, significantly elevated right-sided filling pressures, and low cardiac output indicating worsening right heart failure. Given the need for additional right-sided support, patient was cannulated for ECMO. (V) At the time of Impella removal, haemodynamics had normalized off inotropic support. (VI) At the time of ECMO decannulation, haemodynamics continued to be stable off Impella and inotropic support. (VII) Post-ECMO decannulation, stable haemodynamics continued.

HD, hospital day; PCWP, pulmonary capillary wedge pressure; PAP, pulmonary arterial pressure; RAP, right atrial pressure; TD, thermodilution.

Figure 2 (A) Endomyocardial biopsy with H&E stain at 20× magnification showing lymphocyte predominant infiltration of the myocardium with no eosinophils or giant cells. (B) Timeline showing troponin trend and timing of mechanical support and immunosuppression regimen. Antithymocyte globulin (ATG) dosage 0.75 or 1.5 mg/kg daily titrated to absolute lymphocyte count. Interruptions in plasmapheresis due to coagulopathy and bleeding requiring transfusion while on extracorporeal membrane oxygenation. (C) Cardiac magnetic resonance imaging (CMR) during second admission revealed patchy, predominantly mid myocardial delayed enhancement throughout the left ventricular myocardium suggestive of myocarditis (arrows indicate areas of late gadolinium enhancement). Not shown, CMR obtained on initial admission was negative for delayed gadolinium enhancement. ATG, antithymocyte globulin; ECMO, extracorporeal membrane oxygenation; LV, left ventricle; MRI, magnetic resonance imaging; RV, right ventricle.



of suspicion regardless of timing.[6,7] In this case, the delayed onset 5 months after therapy initiation led to a misdiagnosis.

Diagnosis of ICI-associated myocarditis includes biomarkers, ECG, and imaging evaluation. Troponin elevation is sensitive for ICI-associated myocarditis and is abnormal in 94% of cases.[6] No specific troponin cut-off has been identified, and in fact, troponin rise may be modest with peak Troponin T of 2.68 ng/mL (IQ 0.24–7.63) in patients with major adverse cardiac events (MACE).[6] ECG is abnormal in 89% of cases, and arrhythmias include conduction delays, atrial, and/or ventricular arrhythmias. Nearly half of patients with ICI-associated myocarditis have a normal LVEF on presentation.[6] Abnormal global longitudinal strain on echocardiography is associated with an increased risk of MACE regardless of LVEF.[8] CMR detects delayed myocardial enhancement and oedema but lacks sensitivity especially early in the disease process (<4 days after presentation).[9] In this case, CMR findings only appeared on repeat imaging late in the clinical course. The current gold standard for diagnosis is EMB, characterized by extensive lymphocytic infiltration of the myocardium. In a proposed framework for diagnosis of ICI-associated myocarditis, definite myocarditis like this case includes either (i) tissue pathological confirmation on EMB or autopsy or (ii) abnormal imaging on CMR or echocardiogram in the appropriate clinical scenario with abnormal biomarker and/or ECG findings. Diagnoses of 'probable' or 'possible' myocarditis include scenarios with isolated imaging, biomarker, or ECG findings.[10]

The tenants of treatment of ICI-associated myocarditis are immunosuppression, supportive care, and stopping ICI therapy. No randomized controlled trials have assessed ICI-associated myocarditis treatments, but corticosteroids are the cornerstone of treatment. In uncomplicated ICI-associated myocarditis, oral prednisone (1–2 mg/kg) is

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recommended; in severe or refractory cases, such as this patient, high-dose IV methylprednisolone (500 mg to 1 g daily) is preferred.[11] An international, multicentre registry study showed that early administration (<24 h) and high doses (500–1000 mg per day) of corticosteroids were associated with decreased risk of MACE.[12] In severe or steroid-resistant ICI-associated myocarditis, additional agents target the cellular immune response including mycophenolate mofetil, antithymocyte globulin (antithymocyte globulin), and rituximab.[6,11,13] Dosing and use of these agents have been largely adapted from transplant rejection protocols.

The most novel aspect of this case was the use of advanced temporary MCS. ICI-associated myocarditis can be fatal in up to half of those affected, and approximately, half of survivors will not have recovery of cardiac function.[6,7] Unlike other causes of myocarditis, these patients inherently have underlying malignancies and comorbidities that may lead to avoidance of aggressive interventions and ineligibility for advanced therapies such as heart transplants or durable ventricular assist devices. However, unlike most causes of myocarditis, particularly viral myocarditis, ICI-associated myocarditis is effectively treated with immunosuppression, which may hasten cardiovascular recovery. It is therefore reasonable to pursue temporary MCS as a bridge to recovery. MCS options in this case of profound cardiogenic shock included intraaortic balloon pump, Impella, Tandem Heart (LivaNova PLC, London, UK), and VA-ECMO. High-quality randomized data for comparison of MCS devices is limited. Two prior cases in the literature report the use of VA-ECMO in ICI-associated myocarditis, but there are no reports of isolated or concomitant Impella use ('ECPELLA').[14,15] Due to primarily left heart failure, without need for maximal mechanical or respiratory support, the decision was made to proceed with Impella support. Despite this and maximal inotropic support, ongoing myocarditis led to worsening biventricular failure, requiring escalation to VA-ECMO. With appropriate immunosuppression, patient was weaned off mechanical support.

The risks of restarting ICI therapy are unknown, but guidelines recommend always holding ICIs and permanently discontinuing for cardiotoxicity more than grade I (asymptomatic biomarker elevation).[11] Plasmapheresis removes ICI antibodies in severe cases given the long half-life of ICIs (14.5 to 27.0 days).[16]

Knowledge of the presentation and treatment of ICI-associated myocarditis is evolving, but it can be elusive to diagnose. Our case underscores the critical need for multidisciplinary approaches for rapid identification and treatment for this unique patient population, particularly in fulminant myocarditis complicated by cardiogenic shock. Further study is needed regarding which patients with ICI-associated myocarditis will benefit from MCS given the unique dilemma of prognosis of their concomitant malignancy.

Conflict of interest

None declared.

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