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CLINICAL CASE CHALLENGES

Delayed Diagnosis and Recovery of Fulminant Immune Checkpoint Inhibitor-Associated Myocarditis on VA-ECMO Support

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CASE

A 50-year-old woman with metastatic cervical cancer presented to the emergency department with a 1-week history of dyspnea on exertion and chest pain. She received etoposide, carboplatin, and atezolizumab 21 days prior; atezolizumab was started 42 days prior. The initial evaluation revealed no pulmonary embolism or pneumonitis, inferior Q waves, a peak troponin I of 1.4 ng/mL (normal < 0.32 ng/mL), and brain natriuretic peptide of 11 pg/mL (normal 10-100 pg/mL). A transthoracic echocardiogram (TTE) showed a normal left ventricular ejection fraction (LVEF) of 60% with basal- and mid-anteroseptal and -inferoseptal wall hypokinesis. Left heart catheterization showed no obstructive coronary artery disease. Her symptoms were attributed to coronary vasospasm, and she was discharged home.

Over the next 10 days, she presented to 2 separate emergency departments 3 times and was also readmitted once. Eight days after her initial presentation, high-sensitivity troponin I (hsTnI) rose to 2,119.3 ng/L (normal: <17 ng/L). N-terminal pro-B-type natriuretic peptide (NT-proBNP) was 725 pg/mL (normal: <300 pg/mL). A repeat TTE showed no significant changes. Because of concerns for coronary microvascular dysfunction, coronary vasospasm, and pericarditis, she was treated with calcium-channel blockers, nonsteroidal anti-inflammatories, and colchicine.

She had mild improvement in cardiac symptoms but developed diplopia. She underwent neurologic evaluation with brain magnetic resonance imaging, lumbar puncture, and serologic testing, which were negative for infectious, inflammatory, ischemic, or structural etiologies. She was scheduled to follow-up with ophthalmology as an outpatient for mild persistent symptoms.

One month later, her restaging scans showed no evidence of disease. However, she complained of worsening dyspnea, chest tightness, and lower extremity edema and was transferred to our institution for further evaluation. Her electrocardiogram showed poor R-wave progression and lateral T-wave inversions. Her hsTnI was lower at 249 ng/L, whereas NT-proBNP rose to 5,174 pg/mL. A TTE showed left ventricular cavity dilation, LVEF of 14%, and severely reduced right ventricular function. Cardiac magnetic resonance (CMR) showed a left ventricular thrombus but no late gadolinium enhancement (LGE). The cardio-oncology service was consulted.

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Given the high suspicion of immune checkpoint inhibitor (ICI) myocarditis, the patient underwent an urgent endomyocardial biopsy that showed lymphocytic myocarditis consistent with ICI myocarditis.

DISCUSSION: INITIAL DIAGNOSIS

ICIs are monoclonal antibodies used to treat an increasing number of malignancies, significantly improving outcomes compared with standard chemotherapy. ICIs inhibit the following host immune negative regulation receptors: programmed cell death ligand 1 (atezolizumab, avelumab, and durvalumab), programmed cell death protein 1 receptor (nivolumab, pembrolizumab, cemiplimab, and dostarlimab), cytotoxic T-lymphocyte-associated protein 4 receptor (ipilimumab), and lymphocyte-activating gene 3 (relatlimab). ICI myocarditis is an uncommon (~1%) immune-related adverse event (IRAE) compared with IRAEs such as cutaneous toxicities (71.5%) and colitis (8%-27%); however, it is associated with a 46% mortality rate.[1-3] Survival outcomes do not differ significantly in patients who have had ICIs discontinued because of IRAEs.[4]

Although symptoms and severity vary, ICI myocarditis presentation commonly involves chest pain (37%) and electrocardiographic abnormalities (89%), with a median presentation time after ICI therapy initiation of 30 days.[1-3] Cardiac biomarker elevation and arrhythmias are common; myositis and myasthenia-like symptoms such as diplopia can also occur.[1,2] Half of ICI myocarditis cases are associated with normal LVEF.[5] In patients treated with ICIs, persistent cardiac symptoms and elevated biomarkers should increase the suspicion for ICI myocarditis. Our patient first presented with chest pain, electrocardiographic changes, biomarker elevations, and normal LVEF. Left heart catheterization appropriately ruled out acute coronary syndrome. Undiagnosed and untreated for over 7 weeks, her LVEF decreased to 14% with a concomitant hsTnI decrease. The relative hsTnI drop but lack of resolution likely represented persistent subacute inflammation with progressive myocardial injury and adverse remodeling; a "burnt-out," dilated cardiomyopathy; and heart failure. However, ICI myocarditis was not considered, underscoring the need for additional education outside of cardio-oncology.

To diagnose ICI myocarditis, CMR is the preferred imaging modality because of the added resolution and tissue characterization. To detect acute myocarditis on CMR, the 2018 Lake Louise criteria use T1 mapping, T2 mapping, LGE, and extracellular volume.[5,6] Lake Louise criteria are estimated to be 88% sensitive and 96% specific. Nevertheless, in an ICI myocarditis registry, LGE was present in 48% and T2 elevation in 28%.[5] In our case, the delayed presentation with only LGE available contributed to reduced test sensitivity. We obtained the gold standard for diagnosing myocarditis, an endomyocardial biopsy, which typically shows infiltration of T cells, macrophages, and myocyte death.

CASE CONTINUED

The patient was given intravenous (IV) methylprednisolone 1,000 mg for ICI myocarditis. Unfortunately, she suffered a cardiac arrest the following morning because of unstable ventricular arrhythmias. Spontaneous circulation returned after 8 minutes of cardiopulmonary resuscitation. She was intubated and transferred to the intensive care unit. Hypotensive with continued ventricular arrhythmias, she was started on epinephrine, amiodarone, and then lidocaine. She developed further hemodynamic deterioration throughout the day, requiring 3 vasopressors. She had limited urine output, metabolic acidosis, and worsening cardiac index by Swan-Ganz catheter. After a multidisciplinary discussion that included critical care, cardio-oncology, advanced heart failure, and cardiac surgery, venoarterial extracorporeal membrane oxygenation (VA-ECMO) was offered as a bridge to recovery. The family agreed that this was aligned with her goals.

DISCUSSION: HEMODYNAMIC SUPPORT

Significant hemodynamic supportive care can be required in fulminant ICI myocarditis. VA-ECMO was the only option for our patient with rapidly declining hemodynamic status. Support with IV inotropic support or an intra-aortic balloon pump was considered insufficient given the patient's trajectory. Impella (Abiomed)

ABBREVIATIONS AND ACRONYMS

CMR = cardiac magnetic resonance

hsTnI = high-sensitivity troponin I

ICI = immune checkpoint inhibitor

IRAE = immune-related adverse event

IV = intravenous

IVIG = intravenous immunoglobulin

LGE = late gadolinium enhancement

LVEF = left ventricular ejection fraction

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

TTE = transthoracic echocardiogram

VA-ECMO = venoarterial extracorporeal membrane oxygenation

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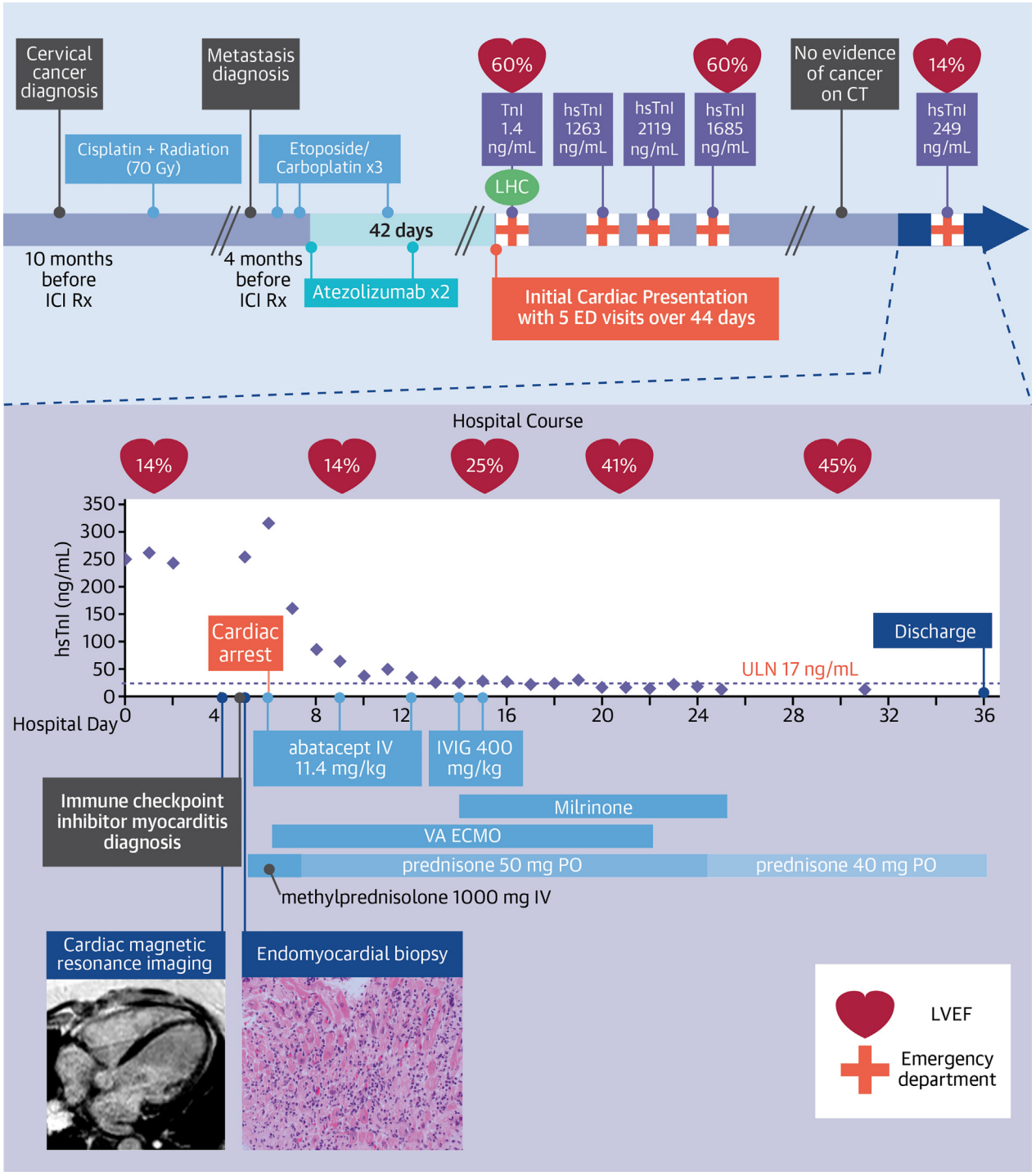
FIGURE 1 **Immune Checkpoint Inhibitor Myocarditis Clinical Course**



The time line shows cancer treatment with immune checkpoint inhibitor (ICI) through ICI myocarditis therapy. Cardiac magnetic resonance shows a 4-chamber long-axis phase-sensitive inversion recovery image of severe biventricular dysfunction without late gadolinium enhancement. Endomyocardial biopsy shows lymphocytic infiltration and myocardial necrosis. CT = computed tomography; ED = emergency department; hsTnI = high-sensitivity troponin I; IV = intravenous; IVIG = intravenous immunoglobulin; LHC = left heart catheterization; LVEF = left ventricular ejection fraction; PO = by mouth; ULN = upper limit of normal; Rx = medical prescription; VA-ECMO = venoarterial extracorporeal membrane oxygenation.

support was contraindicated because of left ventricular thrombus. Two cases of ICI myocarditis requiring VA-ECMO are reported in the literature; one was fatal, and the other needed 2 days of support.[7,8]

Offering VA-ECMO without the option of destination therapy such as a left ventricular assist device or heart transplant given her recent metastatic cancer diagnosis can be fraught. Multidisciplinary discussions with the patient and family about care goals are critical. Although her malignancy had an excellent response with no evidence of disease on recent surveillance imaging, her anticipated cancer treatment was held because of her acute cardiac decompensation. The long-term cancer prognosis remained uncertain, and long-term cardiac impairment could limit future cancer therapy options if needed. Comorbidities and frailty were also considered. Working as a teacher through cancer therapy, our patient was very active before her acute cardiac decompensation. Aggressive supportive care was in line with her goals and appropriate from a medical perspective.

CASE CONTINUED

After femoral cannulation for VA-ECMO, her hemodynamic parameters, acidosis, and urine output progressively improved. She was extubated the following day. Her immunosuppression regimen consisted of 3 days of IV methylprednisolone and then a prednisone taper starting at 60 mg daily. Because of her acute decompensation and tenuous status, we also initiated IV abatacept 11.4 mg/kg (1,000 mg) on the day of her cardiac arrest. An interval TTE showed no improvement in LVEF after 4 days on VA-ECMO despite a rapid decrease in hsTnI. She received additional abatacept on days 4 and 7 postarrest plus intravenous immunoglobin (IVIG) 400 mg/kg over 2 days (day 9 and 10 postarrest) for a total of 70,000 mg. Her hsTnI decreased to the normal range at 14 ng/L. NT-proBNP decreased to 7,357 pg/mL after peaking at 12,578 pg/mL.

DISCUSSION: IMMUNOSUPPRESSION

Based on the guidelines for suspected ICI myocarditis, the patient was treated with IV methylprednisolone 1,000 mg daily for 3 days followed by a 4- to 6-week prednisone taper.[3] For prolonged high-dose steroid regimens, stress ulcers, pneumocystis prevention, and vitamin D/calcium supplementation are important. However, when and if to initiate additional immunosuppressive therapies remains controversial. More aggressive therapy initiation must be weighed against the opportunistic infection risk. Immunohistochemistry staining in ICI myocarditis identified a wide array of immune targets, including T-cell markers (CD3, CD4, CD8, and FOXp3), B-cell markers (CD20), macrophage markers (CD68), and programmed death ligand 1. Case reports show successful use of therapies targeting these mechanisms, including abatacept, antithymocyte globulin, alemtuzumab, tocilizumab, mycophenolate mofetil, IVIG, and plasmapheresis.[1,5,9,10] Larger data sets and clinical trials are needed to guide optimal immunosuppressive regimens. The ATRIUM (Abatacept in Immune Checkpoint Inhibitor Myocarditis) study is a randomized placebo-controlled trial evaluating whether abatacept can reduce major adverse cardiac events (NCT05335928). Our patient would not have been a candidate for ATRIUM because of her cardiac arrest.

In our case, we started IV methylprednisolone on the same day as her biopsy followed by a steroid taper with prednisone 60 mg daily, which is lower than published recommendations but consistent with our institutional practice.[3] Because of illness severity, we chose additional immunosuppression. We considered antithymocyte globulin for potent immunosuppression given its use in heart transplant rejection, but we were concerned with infection risk. We chose to treat her with abatacept, a cytotoxic T-lymphocyte–associated protein 4 agonist that works directly in opposition to ICIs. hsTnI biomarker immediately improved after IV methylprednisone and abatacept. However, there was no significant clinical change based on LVEF, and whether she needed additional immunosuppression was an ongoing concern. Given the biomarker improvement, the cardio-oncology team thought she had received sufficient T-cell–directed therapy and decided to cover B-cell–mediated immunosuppression with IVIG. Whether this therapy provided additional benefit is not clear.

CASE CONTINUED

Heparin-induced thrombocytopenia complicated her course. She also developed melena, likely related to friable colonic tissue from prior pelvic radiation, that required blood transfusions and anticoagulation interruption. Through this, the patient remained hemodynamically stable with an appropriate mental status and

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renal function. After extensive multidisciplinary discussions with the patient and the family, aggressive supportive care was pursued despite uncertainty about the probability and timeline for recovery.

Milrinone was started, and a subsequent TTE showed mild improvement of LVEF to 25%. Bleeding resolved after argon beam coagulation during colonoscopy, and anticoagulation was resumed. After 16 days on VA-ECMO, her LVEF improved to 41%, and she was sustained on lower ECMO support. She underwent decannulation 2 days later. A repeat TTE showed an improved LVEF of 45% off inotropic support and on guideline-directed medical therapy. After 36 days of hospitalization, she was discharged to an acute rehabilitation facility for 10 days before returning home, where she continued physical therapy. She noted the resolution of diplopia during rehabilitation. The patient's complete course is summarized in **Figure 1**.

SUMMARY

Our patient was diagnosed with ICI-associated myocarditis 7 weeks after the initial cardiac symptoms with a subsequent decline in LVEF from 60% to 14%. CMR was inconclusive for myocarditis based on LGE. Endomyocardial biopsy established the diagnosis of ICI myocarditis. She required VA-ECMO support after a cardiac arrest and received aggressive immunosuppression with high-dose corticosteroids, abatacept, and IVIG. Her LVEF recovery on VA-ECMO took place over 2 weeks; LVEF was unchanged at 14% at 4 days, 25% with milrinone at 10 days, and 41% with milrinone at 14 days. Her LVEF recovered to 45% off inotropes before discharge. Our case demonstrates that as ICI therapy use becomes more widespread, education outside of cardiology is critical in order to promote early recognition and treatment. Furthermore, the course of ICI myocarditis, even in severe fulminant disease with a delayed diagnosis, can be favorable with a multidisciplinary team, appropriate hemodynamic support, immunosuppressive therapy, and time.

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