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CARDIO-ONCOLOGY

CASE REPORT: CLINICAL CASE

Elevated Troponin T in Immune-Checkpoint Inhibitor Myositis

A Case of Mistaken Myocarditis

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ABSTRACT

A patient with metastatic renal cell carcinoma on axitinib and pembrolizumab had elevated high-sensitivity cardiac troponin T and normal high-sensitivity cardiac troponin I with unremarkable cardiac investigations. A noncardiac cause (myositis) was the likely cause for cardiac troponin T elevation. Cardiac troponin I may be a more appropriate marker to support a myocarditis diagnosis with concurrent myositis. (JACC Case Rep 2024;29:102462) © 2024 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 61-year-old woman presented with recurrent metastatic renal cell carcinoma to the liver and lungs. She was started on axitinib, a vascular endothelial growth factor tyrosine kinase inhibitor, and pembrolizumab, a programmed cell death protein-1 (PD-1) inhibitor with palliative intent. Before cycle 2, she developed shooting right arm pain and was investigated for coronary disease given her underlying risk factors. She denied shortness of breath and chest pain. Her work-up included an electrocardiogram that was unchanged from previous and a high-sensitivity cardiac troponin T (hs-cTnT) of 25 ng/L (overall 99th percentile upper reference limit: ≤14 ng/L on the Roche hs-cTnT assay). Two days later, a high-sensitivity cardiac troponin I (hs-cTnI) collected in the community was 27 ng/L (overall 99th percentile upper reference limit: <45 ng/L on the Siemens Atellica hs-cTnI assay). Her creatine kinase (CK) was elevated (236 U/L; reference range: 30-200 U/L). A week later, her oncologist sent her to the emergency department (ED) because of worsening shortness of

LEARNING OBJECTIVES

- To understand the discordance between cTnT and cTnI levels when investigating concurrent ICI-associated myocarditis in the context of ICI-associated myositis.
- To identify potential causes of elevated cTnT in patients with ICI-associated myositis.

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ABBREVIATIONS AND ACRONYMS

CK = creatine kinase

cTnT = cardiac troponin T

ED = emergency department

hs-cTnI = high-sensitivity cardiac troponin I

hs-cTnT = high-sensitivity cardiac troponin T

ICI = immune checkpoint inhibitor

irAE = immune-related adverse event

PD-1 = programmed cell death protein-1

Tnt = troponin T

breath, an increasing hs-cTnT, and a concern of pulmonary embolism. Her blood pressure was 132/93 mm Hg, pulse was 66 beats/min, respiratory rate was 18 breaths/min, oxygen saturation was 99% on room air, and temperature was 36 °C. She was evaluated by the ED physician and by the cardiology service. She had an unremarkable physical examination and normal hemoglobin, platelet count, leukocyte count, kidney function, and liver enzymes. N-terminal pro-B-type natriuretic peptide was 304 ng/L (normal: <125 ng/L). Her C-reactive protein was 2.8 mg/L (normal: <8.0). She had further elevations in hs-cTnT (64 to 77 ng/L) and CK (298 and 757 U/L). Her electrocardiogram showed no acute changes to suggest ischemia. Computed tomography pulmonary angiography did not find pulmonary embolism. She was discharged home.

A week later, she continued to have dyspnea, arm pain, new diplopia, joint pain, and proximal leg pain and weakness limiting her functioning. She had normal C-reactive protein but elevated CK (1,676 U/L) and aspartate aminotransferase (85 U/L; reference range: <45 U/L) and alanine aminotransferase (104 U/L; reference range: <50 U/L). She was diagnosed with grade 2 immune checkpoint inhibitor (ICI)-associated myositis and started on prednisone 50 mg daily with rapid improvement in her symptoms.

She was referred to the ED due to unilateral facial drooping, and her brain computed tomography and magnetic resonance imaging did not identify intracranial abnormalities. Repeat hs-cTnT increased to 168 ng/L. Her dipyridamole stress myocardial perfusion imaging demonstrated no ischemic perfusion abnormalities, and her cardiac magnetic resonance showed no evidence of myocarditis or significant valvular dysfunction. Her left ventricular ejection fraction was 52%. Her serum tested negative for a series of myositis-related autoantibodies.

PAST MEDICAL HISTORY

She had a history of mild left ventricular dysfunction (left ventricular ejection fraction 45%-50%), dyslipidemia, diabetes, hypertension, atrial fibrillation, acid reflux, and anxiety. She had a radical nephrectomy and adrenalectomy 10 years prior for renal cell carcinoma.

INITIAL MANAGEMENT

The rheumatology service was unable to provide a definitive diagnosis of ICI-associated myositis at the time of assessment because the proximal muscle symptoms had resolved. Her hs-cTnT continued to increase to 384 ng/L (**Figure 1**). Although she did not meet the diagnostic criteria for ICI myocarditis,[1] without an alternative explanation for her rising hs-cTnT, the cardio-oncology service diagnosed her with smoldering myocarditis. Prednisone dose was increased back to 75 mg (1 mg/kg) daily for 4 days. Unfortunately, she developed steroid-induced mania and required admission to the psychiatry inpatient service. Prednisone dose was then decreased to 30 mg daily, and she was started on steroid sparing oral mycophenolate mofetil 1,000 mg twice a day. At this point, her hs-cTnT began decreasing.

INVESTIGATIONS

Given the discordance between her hs-cTnT levels and cardiac symptoms, we sought to further investigate the possibility of a laboratory confounder. Initial laboratory investigation consisted of rerunning 2 of the patient's previously collected blood samples on the Siemens Atellica hs-cTnI, Beckman hs-cTnI, and/or Abbott i-STAT conventional cTnI assays. **Table 1** demonstrates hs-cTnI levels below the 99th percentile upper reference limit on all 3 assays despite an elevated hs-cTnT having been measured for each sample.

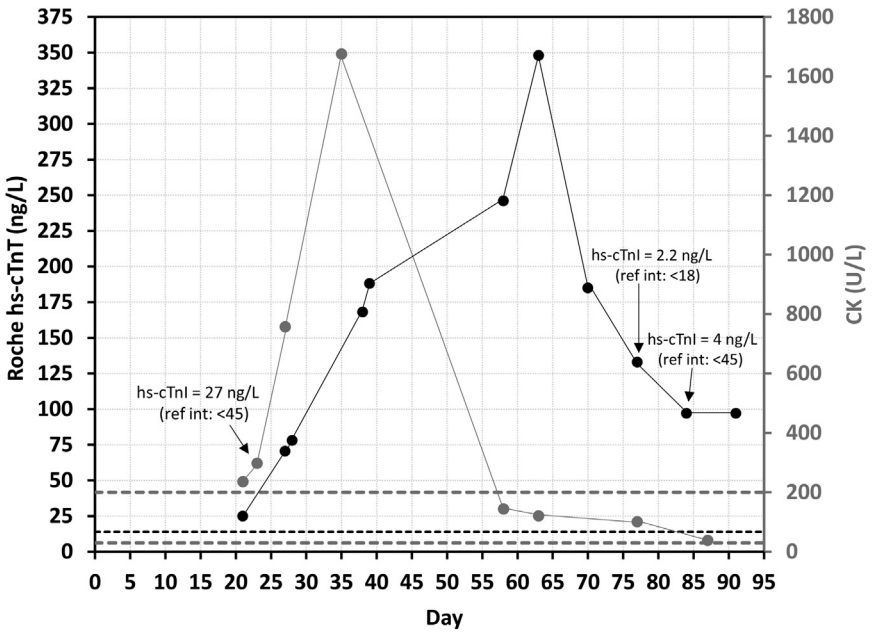
DIFFERENTIAL DIAGNOSIS

Potential interpretations of troponin discordance include the following:[2] 1) falsely elevated hs-cTnT with truly negative hs-cTnI (ie, no cardiomyocyte injury); or 2) truly elevated hs-cTnT with falsely negative hs-cTnI (ie, cardiomyocyte injury). The suspicion based on the clinical information was that there was no cardiomyocyte injury. Potential causes of troponin discordance include renal dysfunction, skeletal troponin T (TnT) cross-reactivity, cardiac troponin T (cTnT) re-expression in injured skeletal muscle, macrotroponin, and analytical interference with the hs-cTnT assay including heterophile antibody, autoantibodies, elevated rheumatoid factor, and a pathologic anti-ICI antibody.

FURTHER LABORATORY ANALYSIS

Analyzer malfunctions and reagent issues were ruled out by reviewing quality control testing and troubleshooting logs for the days when the patient's sample had been tested for hs-cTnT. There was no significant hemolysis, icterus, or lipemia in any of the patient's hs-cTnT samples as demonstrated by serum indices. The patient also had normal kidney function, ruling

FIGURE 1 High-Sensitivity Cardiac Troponin T and CK Trends



The straight lines connecting individual points are included to facilitate visual assessment of the results. They do not represent the actual rate of change for troponin and CK observed in this patient. CK = creatine kinase; hs-cTnI = high sensitivity cardiac troponin I; hs-cTnT = high-sensitivitiy cardiac troponin T; ref int = 99% upper reference limit.

out renal dysfunction as a confounding factor. Rheumatoid factor was normal. The presence of macrotroponin T was investigated with 2 different polyethylene glycol precipitation protocols, but results were inconclusive. A search of peer-reviewed scientific literature did not identify any reports of macrotroponin causing a rise/fall hs-cTn pattern in the absence of concomitant cardiac pathology. Based on these 2 findings together, the presence of macrotroponin T as the sole cause of the patient's rise/fall hs-cTnT pattern was deemed unlikely. Analysis of a blood sample with elevated hs-cTnT using heterophile antibody blocking tubes demonstrated no change in hs-cTnT, suggesting the absence of heterophile antibodies. The presence of human anti-animal antibody and autoantibodies could not be ruled out directly, but their presence is expected to cause a constant elevation in hs-cTnT instead of a rise/fall pattern. Spiking of a normal patient plasma pool with pembrolizumab did not yield an elevated hs-cTnT result, thus eliminating ICI immunoglobulin as a possible interferent. Finally, skeletal TnT cross-reactivity with the hs-cTnT assay could not be ruled out directly; however, it seemed a likely possibility given the patient's myositis.

DISCUSSION

This case highlights the diagnostic challenges clinicians face in diagnosing ICI-associated myocarditis, particularly in a patient with rising cardiac troponins

TABLE 1 hs-cTnT and hs-cTnI Results for 2 of the Patient's Blood Samples

	Roche hs-cTnT, ng/L	Beckman hs-cTnI, ng/L	Siemens hs-cTnI, ng/L	Abbott i-STAT cTnI, μg/L
Sample 1	133	2.2	Not tested	Unavailable[a]
Sample 2	97	Not tested	4	Unavailable,[b] 0.00
99th percent upper reference limit	<14	<18	<45	≤0.04

[a]i-STAT device gave a cartridge error for 2 different testing attempts. [b]i-STAT device gave a cartridge error for 1 of 2 testing attempts.

cTnI = cardiac troponin I; hs-cTnI = high-sensitivity cardiac troponin I; hs-cTnT = high-sensitivity cardiac troponin T.

with no clear cardiac symptoms and unremarkable cardiac magnetic resonance. Moreover, this case illustrates the importance of understanding the difference between hs-cTnT and hs-cTnI assays in the diagnosis of ICI-associated myocarditis.

Immune-related adverse events (irAEs) with PD-1/programmed death-ligand 1 inhibitors have a reported incidence of 27%.[3] Among irAEs, PD-1 inhibitor-induced myositis has an incidence of 0.38%[4] and myocarditis has an incidence of 0.3% to 0.5%.[3] Among those with myositis, 16.1% also have myocarditis.[5] ICI-associated myocarditis is a rare but life-threatening irAE, with estimated incidence of up to 1% and mortality rates up to 50% reported in the fulminant myocarditis group.[3] ICI-associated myocarditis exists along a clinical and histopathologic spectrum, but less is known about the clinical entity of subclinical or smoldering myocarditis.[6] This patient had evidence of myositis in addition to features suggestive of myasthenia gravis, which are risk factors for developing severe myocarditis. These patients require close monitoring and prompt treatment to avoid serious complications due to a potentially high fatality rate.[7]

The diagnosis of ICI-associated myocarditis can be challenging because traditional diagnostic criteria for myocarditis were established in viral myocarditis rather than ICI-associated myocarditis, and because proposed criteria for ICI-associated myocarditis have not been validated to date.[1] The absence of late gadolinium enhancement on cardiac magnetic resonance does not exclude ICI-associated myocarditis because studies have shown that late gadolinium enhancement is found in <50% of patients with ICI-associated myocarditis compared with >80% in non–ICI-associated myocarditis.[1,8]

High-sensitivity cardiac troponin testing is suggested for the diagnosis of patients undergoing ICI treatment.[3] Schmid et al[9] demonstrated that among patients with skeletal myopathies, hs-cTnT was elevated in 69% of patients, whereas hs-cTnI was only elevated in 4.1% of patients. These results suggest that either cross-reactivity of skeletal TnT in hs-cTnT assays or cTnT expression in injured skeletal muscle[10] are the main explanations for troponin elevation in these patients; however, the exact mechanism and contribution of each is unclear. The present case demonstrates that this relationship could also apply to ICI-associated myositis because either skeletal TnT cross-reactivity or cTnT expression in injured skeletal muscles could have resulted in the elevated hs-cTnT but not hs-cTnI in this patient. However, we cannot rule out that hs-cTnT is a more sensitive marker of ICI-associated myocardial injury/inflammation compared with hs-cTnI, and that the magnitude of myocardial injury/inflammation in this patient could not be detected by cardiac magnetic resonance.

There are only 2 reports in the literature, both in patients with melanoma, of ICI-associated myositis with significant hs-cTnT elevation but with proportionally less elevated[11] or normal[12] hs-cTnI. The present case is the first to show this hs-cTnT and hs-cTnI discordance in a patient with metastatic renal cell carcinoma on pembrolizumab. The present case highlights the role of interpreting both hs-cTnT and hs-cTnI results when considering the diagnosis of ICI-associated myositis and concurrent myocarditis. Discordant results require the consideration of other explanations such as laboratory confounders. A multidisciplinary approach involving cardiology, oncology, and medical biochemistry is suggested to differentiate these 2 irAEs.

FOLLOW-UP

In the context of the aforementioned investigations, either skeletal TnT cross-reactivity or cTnT expression in injured skeletal muscles was the cause of elevated hs-cTnT. The patient's mycophenolate mofetil was discontinued, and she was placed on an oral prednisone taper. Her psychiatric symptoms stabilized during her admission. She was eventually restarted on axitinib without pembrolizumab.

CONCLUSIONS

This case demonstrates the importance of using a multidisciplinary systematic approach when there is a discrepancy between hs-cTnT and hs-cTnI to identify the underlying cause, which may include measuring an alternate assay to make an appropriate diagnosis.

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