

False-positive Troponin I Assay elevation due to occult Mixed Cryoglobulinemic Vasculitis

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A 53-year-old man with active hepatitis C and cirrhosis presented with a vasculitic rash, myalgias, and fatigue, and was found to have an elevated cardiac troponin I up to 15.7 ng/mL with normal electrocardiogram, echocardiogram, and coronary angiogram prior to being discharged. Subsequently, during a similar presentation to another academically affiliated hospital, the patient had a normal cardiac troponin T (< 0.01 ng/mL). Upon his third presentation with significantly elevated troponin I to 15.98 ng/mL, the patient was found to have cryoglobulinemic vasculitis and elevated rheumatoid factor due to active hepatitis C, causing interference with the troponin I immunoassay. In conclusion, troponin I assays may have high false-positive values due to interference by rheumatoid factor and/or a polyclonal antibody found in cryoglobulinemia.

Keywords

Biomarkers; Troponin; Cryoglobulinemia; Acute coronary syndrome

1. Introduction

A 53-year-old man with cirrhosis secondary to hepatitis C virus and alcoholism, hypertension, multidrug abuse including tobacco and methamphetamines, and chronic pain/neuropathy presented to the San Diego Veterans Affairs Emergency Department with diffuse body aches, fatigue, and weakness. The patient reported chronic left shoulder and right hip pain, vague in nature, that had been ongoing over the past year despite treatment with ibuprofen, gabapentin, and venlafaxine. His vital signs were within normal limits. His physical examination was notable for slight pitting edema in both lower extremities, and a diffusely scattered, bilateral lower-extremity, dark purple, non-blanching, palpable rash consistent with purpura and petechiae. Laboratory testing showed a normal white blood cell count, slight normocytic anemia with a hemoglobin of 11 g/dL, thrombocytopenia of 89 1000/mm³, elevated erythrocyte sedimentation rate (ESR) of 77 mm/h, normal C-reactive protein of 0.8 mg/dL, aspartate aminotransferase of 54 U/L, alanine aminotransferase of 75 U/L, international normalized ratio of 1.4, normal electrolytes, blood urea nitrogen of 12 mg/dL,

creatinine of 0.4 mg/dL, and a cardiac troponin I of 7.6 ng/mL (ADVIA Centaur® TnI-Ultra® assay [Siemens Medical Solutions USA, Malvern, PA], 99th percentile cut-point < 0.07 ng/mL), that increased to 13.3 ng/mL, then 15.98 ng/mL 3 and 6 hours later, respectively. The patient had two electrocardiograms, 4 hours apart, that were both normal. His chest radiograph showed slight pulmonary edema with no consolidation.

Upon further review of the patient's medical record, it was discovered that 3 days prior to this presentation, the patient was evaluated at the University of California San Diego Hillcrest Emergency Department for his chronic diffuse pain and was found to have a normal troponin T (< 0.01 ng/mL) with a normal electrocardiogram. Additionally, he had a similar presentation to the Veterans Affairs Emergency Department 2 weeks prior, with diffuse body pains and rising cardiac troponin I of 7.6 ng/mL, 14.46 ng/mL, and 15.7 ng/mL at 0, 3, and 6 hours, respectively. During this previous visit, he was admitted for suspicion of a non-ST elevation myocardial infarction (NSTEMI). His coronary angiogram at that time revealed no coronary artery disease at the epicardial level with normal flow, and his echocardiogram was also unremarkable. He was subsequently discharged.

Further laboratory results at Veterans Affairs revealed that the patient had cryoglobulinemia (cryocrit of 4%), complement component 3 (C3) of 87 mg/dL (normal, 90-180 mg/dL), complement component 4 (C4) of 9 mg/dL (normal, 16-47 mg/dL), rheumatoid factor of 397 IU/mL (normal, < 14 IU/mL), immunoglobulin G (IgG) of 2391 mg/dL (normal, 740-1400 mg/dL), immunoglobulin A (IgA) of 357 mg/dL (normal, 83-407 mg/dL), immunoglobulin M (IgM) of 853 mg/dL (normal, 34-213 mg/dL), and hepatitis C viral load of 2,300,000 IU/mL, with negative antinuclear antibody (ANA), anti-neutrophil cytoplasmic antibodies, serine protease-3, and myeloperoxidase. The patient was diagnosed with mixed cryoglobulinemic vasculitis secondary to active hepatitis C. His hepatitis C was successfully treated (sustained viral response) with sofosbuvir, velpatasvir, and ribavirin. The vasculitis is resolving, with occasional flares. His repeat troponin I concentrations have now trended downward to 4.55 ng/mL, within 9 months since his original coronary angiogram, 6 months since he has had undetectable hepatitis C viral load, and 2 months since sustained viral

response.

2. Discussion

This case presents a very high, false-positive cardiac troponin I likely caused by cryoglobulinemia. Our patient's mixed cryoglobulinemia was producing polyclonal antibodies, one of which was rheumatoid factor, a common antibody produced in cryoglobulinemic vasculitis (Bonacci et al., 2017). Rheumatoid factor and other such endogenous antibodies as heterophile antibodies, have been described as a cause of false-positive cardiac troponin I values with first-generation assays, such as the AxSYM cTnI assay (Abbott Laboratories, Abbott Park, IL) (Bonacci et al., 2017). See Table 1, for a list of other interfering antibodies and affected assays. The ADVIA Centaur® TnI-Ultra® assay (Siemens Medical Solutions USA) is the troponin I immunoassay utilized at San Diego Veterans Affairs, whereas the cardiac troponin T at UC San Diego was measured with the Elecsys e411 Troponin T high sensitivity on the Cobas e600 system (Roche Diagnostics, Indianapolis, IN). The former using one capture and two detection antibodies, while the later used assays use one capture and detection antibody (Christenson et al., 2017; FDA, 2019)

Cryoglobulinemia has been found to cause false-positive results during serologic tests for syphilis and hepatitis C; however, it has yet to be described as a cause of false-positive cardiac troponin I (Van et al., 1994; Jones et al., 1983). It is unknown to us if the rheumatoid factor or another polyclonal antibody from the cryoglobulinemia caused the false-positive troponin I. Makaryus and colleagues have recommended ultracentrifugation, heterophilic blocking tubes, immunoglobulin-inhibiting reagents, or precipitation with polyethylene glycol to prevent endogenous antibodies from causing troponin immunoassay interference, whereas newer troponin assays have non-specific blocking antibodies to prevent endogenous antibody interference (Makaryus et al., 2007; Tanindi and Cemri, 2011). Unfortunately, in our case, we were unable to simultaneously analyze the patient's blood using two different troponin assays to demonstrate different results. However, his overall presentation, including negative coronary angiogram and down-trending troponin I levels post-hepatitis C treatment lends strong support to his elevated cardiac troponin I being a false-positive result.

Troponin assays are frequently used to rule out acute myocardial infarction; thus, it is essential for providers to understand the many causes of false-positive results to minimize diagnostic errors and any unnecessary interventions. While this case represents one limitation of the cardiac troponin I assay, it also highlights the importance of physician biases-specifically confirmation bias. The patient here presented with diffuse left shoulder pain interpreted as an angina equivalent, and the rising cardiac troponin I pattern led to the incorrect diagnosis of an NSTEMI. However, due to this bias there was no explanation of his chronic pain, fatigue, and lower extremity vasculitic rash, also known as Meltzer's Triad, that is classically seen with cryoglobulinemic vasculitis (Motyckova and Murali, 2011). Although laboratory testing is important to confirm clinical suspicion, it should not supplant our history, physical examination, or clinical acumen.

Table 1. Interfering antibodies and affected troponin assay. Note, this is not a comprehensive table. (Savukoski et al., 2012; Lum et al., 2007; Daniel et al., 2017; Fortgens and Omar, 2013; Ghali et al., 2012)

Interfering Antibody	Troponin Assay
Heterophile Antibodies	CARDIAC Troponin T Quantitative test
	Abbott AxSYM cTnI assay
	Roche Elecsys E17
Auto-antibodies to cardiac troponin	Multiple investigational assays 10 Abbott Architect hs-cTnI assay 12
Rheumatoid Factor	Abbott AxSYM system
	Bayer Immuno I analyzer 11

3. Conclusions

Cardiac troponin I assays may have high false-positive values due to interference by rheumatoid factor and/or a polyclonal antibody found in cryoglobulinemia.

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Conflict of Interest

The authors declare no competing interests.

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