

## Case Report

# Persistent Troponin Elevation in the Setting of an Elevated Rheumatoid Factor: When It Pays to Double Check

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### ABSTRACT

A 78-year-old woman presented twice with high sensitivity troponin I (hs-TnI) elevation. Two cardiac catheterizations showed nonocclusive coronary artery disease, and 2 cardiac magnetic resonance imaging scans were normal. With these investigations unable to explain the troponin I (hs-TnI) elevation, alternate troponin samples were sent to check for assay interference. Results from these troponin assays were low. With the patient having elevated rheumatoid factor as a potential contributor to assay interference, the lab reanalyzed the samples using heterophile antibody blocking tubes, revealing lower hs-TnI levels. This case serves as a reminder to consider assay interference when the clinical picture is inconsistent with ischemia.

### RÉSUMÉ

Une femme de 78 ans a eu deux fois une hausse de la troponine I à haute sensibilité (TnI hs). Deux cathétérismes cardiaques ont montré une coronaropathie non obstructive, et deux examens d'imagerie cardiaque par résonance magnétique se sont révélés normaux. Devant l'incapacité de ces examens à expliquer la hausse de la troponine I (TnI hs), d'autres échantillons de troponine ont été envoyés pour vérifier les interférences sur le dosage. Les résultats de ces dosages de la troponine étaient faibles. Puisque la présence d'un facteur rhumatoïde élevé chez la patiente a possiblement contribué à l'interférence du dosage, le laboratoire a soumis l'échantillon à une nouvelle analyse au moyen de tubes bloquant les anticorps hétérophiles. Cette dernière analyse a mis en évidence des concentrations plus faibles de TnI hs. Ce cas rappelle de tenir compte de l'interférence du dosage lorsque le tableau clinique n'est pas compatible avec l'ischémie.

### Case

A 78-year-old woman with a history of hypertension, dyslipidemia, and rheumatoid arthritis (RA) presented to the hospital with weakness, dizziness, and atypical chest pain. She had no ST changes and high sensitivity troponin I (hs-TnI) elevation (12,850 ng/L, 99th percentile cutoff < 18 ng/L; analytic range: 3–27,000 ng/L, Beckman Access [Beckman Coulter, Indianapolis, IN]), and therefore was admitted and treated as a case of non-ST-elevation myocardial infarction (NSTEMI). Coronary angiogram showed nonocclusive coronary artery disease. Despite this finding, her hs-TnI remained elevated over the next 3 days (11,640 ng/L, 14,470 ng/L, 13,960 ng/L, 14,140 ng/L, 13,160 ng/L, and

12,590 ng/L). This elevation was in contrast with her creatinine kinase (CK) level, which remained lower than the upper limit of normal (< 200 U/L). With the persistent hs-TnI elevation, cardiac magnetic resonance imaging (CMR) was completed to look for inflammation/ischemia. This imaging was negative, and she was discharged as a possible case of myocardial infarction with nonobstructive coronary artery disease. Twenty days later, she presented similarly, and her hs-TnI level was again elevated over 5 days (7210 ng/L, 6600 ng/L, 10,330 ng/L, 10,380 ng/L, 10,290 ng/L, 10,440 ng/L) with a normal CK level. Repeat coronary angiography with optical coherence tomography and CMR did not explain her persistent hs-TnI elevation.

With these investigations unable to explain the hs-TnI elevation, alternate troponin samples were sent to check for assay interference. The sample at our lab (Beckman Access hs-TnI) was high at 10,380 ng/L, and the sample at the other lab (Roche hs-TnT, Roche Diagnostics, Laval, Quebec, Canada) was low (9 ng/L, 99th percentile cutoff < 14 ng/L). Investigations into the source of assay interference revealed that one potential source was her rheumatoid factor (RF), which was elevated to 465 kU/L (reference interval < 20 kU/L). Rheumatology was consulted, and they determined that her

Received for publication November 19, 2020. Accepted February 26, 2021.

**Ethics Statement:** The research reported has adhered to the relevant ethical guidelines.

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See page 983 for disclosure information.

**Novel Teaching Points**

- If the clinical picture is not consistent with ischemia, and the troponin level remains elevated, consider the possibility of assay interference.
- Prior to proceeding to further invasive interventions, consider discussion with laboratory medical colleagues about assay interference.

RA was active, likely because she had discontinued her methotrexate several months prior, secondary to gastrointestinal upset. Rheumatology restarted methotrexate during her admission. Two months after discharge, the RF had decreased to 191 kU/L, and her hs-TnI (Beckman Access) remained moderately elevated but had decreased to 5266 ng/L. Using heterophile antibody blocking tubes, which block human anti-mouse antibodies (although not all heterophile antibodies), the value was reduced further to 3111 ng/L. A comparison hs-TnI assay (Siemens Atellica, Siemens, Munich, Germany) using the same blood sample showed a low value (5 ng/L; 99th percentile cutoff < 45 ng/L). When our lab repeated testing on an up to ×10 dilution using the patient sample, results were nonlinear, indicating the presence of potential interference (Neat = 5266 ng/L; ×2 = 6471 ng/L; ×5 = 9599 ng/L; ×10 = 12,470 ng/L).

**Discussion**

All troponin immunoassays are prone to interferences leading to falsely elevated results (Table 1).<sup>1</sup> A clinician should be prompted to look for evidence of assay interference if a patient presents with an unclear story for ischemia, especially if they have a negative coronary angiography or CMR. In our case, the Beckman Access hs-TnI assay may have been specifically impacted by endogenous interference, such as rheumatoid factor (RF). The patient had several pertinent negatives (no previous infectious mononucleosis,

non-elevated alkaline phosphatase—on each admission, her values were 64-68 units/L, with normal range 30-130 units/L), and no evidence of hemolysis.<sup>2</sup> Additionally, false elevations of troponin due to fibrin clots are minimized with the use of BD Barricor collection tubes (Beckon Dickson (BD), Franklin Lakes, NJ).

The rationale for checking the hs-TnI against another assay is that each troponin assay reacts differently to the heterophilic antibodies,<sup>3</sup> although several other assays are plagued by interference with these antibodies.<sup>4</sup> This interference can be investigated in the laboratory with the use of heterophile antibody blocking tubes. In studies of patients with an elevated RF level, the hs-TnI level was elevated in 3%-15% of patients without myocardial infarction.<sup>1</sup> RF also interferes with several other lab investigations; in our patient’s case, the brain natriuretic peptide level was mildly elevated (117 pg/mL, reference interval <100 pg/mL), but her thyroid-stimulating hormone, ferritin, C-reactive protein, C3, and C4 levels were all normal. CK is also not affected by RF, so this could be checked to help determine if there is evidence of ischemia when troponin assay interference is suspected.

In conclusion, it is important to identify falsely elevated troponin levels. Cases such as this one highlight the subsequent unnecessary admissions, treatment, and invasive testing that can occur when trying to determine the cause of troponin level elevation. Collaboration with the laboratory staff may be helpful to determine if a troponin level elevation is correct, particularly if our clinical evaluation gives us cause to think there may not be true myocardial injury.

**Acknowledgements**

The authors thank the staff at Alberta Precision Laboratories and DynaLIFE Medical Labs.

**Funding Sources**

The authors have no funding to declare.

**Table 1. Common etiologies of troponin elevation**

Etiology of troponin rise			
Cardiac causes	Demand	Noncardiac causes	Assay interference (assay dependent)
<ul style="list-style-type: none"> <li>• Acute myocardial infarction</li> <li>• Myocarditis</li> <li>• Cardiac surgery</li> <li>• Cardiac contusion</li> <li>• Repeated defibrillator shocks</li> <li>• Cardiotoxic agents</li> </ul>	<ul style="list-style-type: none"> <li>• Prolonged tachycardia/bradycardia</li> <li>• Hypertensive urgency</li> <li>• Anemia</li> <li>• Coronary vasculitis</li> <li>• Microvascular dysfunction</li> <li>• Pulmonary embolism</li> <li>• Marathon</li> </ul>	<ul style="list-style-type: none"> <li>• Sepsis</li> <li>• Stroke</li> <li>• Infiltrative diseases</li> </ul>	<ul style="list-style-type: none"> <li>• Biotin supplements</li> <li>• Hemolysis</li> <li>• Previous EBV</li> <li>• Heterophilic antibodies (eg: RF)</li> <li>• Troponin autoantibodies</li> <li>• Fibrin clots</li> <li>• Macro-troponin</li> <li>• Elevated alkaline phosphatase</li> <li>• Elevated lipids</li> </ul>

Data from Mair et al.<sup>1</sup> and Herman et al.<sup>3</sup>  
EBV, Epstein-Barr-virus; RF, rheumatoid factor.

### Disclosures

The authors have no conflicts of interest to disclose.

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