



Case Report

Presence of Macrotrponin for Over 2 Years in a Young Woman

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ABSTRACT

We present the case of a 28-year-old woman who presented with nonspecific symptoms with a high-sensitivity troponin I level > 10,000 ng/L, which led to extensive investigations and a hospital stay. Follow-up testing using an alternate troponin assay yielded undetectable levels. Two years later, the patient had a high-sensitivity troponin I level > 1500 ng/L, with experiments confirming the presence of a macrocomplex. We advocate for communication with laboratory professionals to expedite identification of macrotrponin complexes, so that patients and clinicians can reduce the number of unwarranted investigations. Novel teaching points include the importance of identifying macrocomplexes as a source of persistent false elevations and ensuring that a process is instituted to investigate troponin-level elevations when false-positive results are suspected.

RÉSUMÉ

Nous décrivons le cas d'une femme de 28 ans qui présentait des symptômes non spécifiques et un taux de troponine I mesuré par dosage ultrasensible s'élevant à plus de 10 000 ng/l, ce qui a mené à des investigations poussées et à une hospitalisation. Lors d'analyses de suivi avec une mesure alternative de la troponine, les taux étaient indétectables. Deux ans plus tard, le taux de troponine I mesuré par dosage ultrasensible était supérieur à 1500 ng/l chez cette patiente, et des analyses ont confirmé la présence d'un macrocomplexe. Nous préconisons une communication avec les professionnels de laboratoire pour accélérer la détection de complexes de macrotrponine, afin de permettre aux cliniciens de diminuer le nombre d'investigations qui ne sont pas nécessaires chez les patients. Les points d'enseignements les plus récents insistent sur l'importance de détecter les macrocomplexes qui pourraient être à l'origine des taux de troponine faussement élevés persistants et de s'assurer qu'un processus soit mis en place pour investiguer les élévations du taux de troponine lorsque des résultats faussement positifs sont suspectés.

High-sensitivity troponin assays allow for the precise detection of very low amounts of cardiac troponin and are recommended and incorporated in international guidelines for the diagnosis of myocardial infarction (MI).¹ They are widely used in emergency departments, and can be applied to reliably rule out MI in patients presenting with atypical symptoms, with recommended sex-specific cutoffs.¹

Troponin assays may be subject to interference, resulting in false-positive elevations.²⁻⁴ These false-positive elevations can mislead clinicians to pursue diagnostic tests or treatments that are futile in the absence of MI.^{2,3} This misdirection may result in increased cost, lengthened hospital stays, and harm to the patient.

Two mechanisms for false-positive elevation have been described in the literature.²⁻⁴ Circulating heterophile antibodies may crosslink with either the capture or label antibodies in the absence of troponin, leading to false-positive detection of elevated signaling.² Troponin macrocomplexes are a result of autoantibodies binding to cardiac troponin, leading to reduced clearance and elevated measured troponin level.^{3,4} These interferences can be distinguished by laboratory analysis and investigated when false-positive elevations are suspected.³

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See page 1014 for disclosure information.

Novel Teaching Points

- Troponin macrocomplexes can lead to false-positive troponin-level elevations, leading to unnecessary investigations and prolonged hospital admission.
- Troponin macrocomplexes can persist for several years, which may contribute to ongoing false-positive troponin-level elevations in future encounters.
- A process to investigate elevated troponin-level results when false-positive elevations are suspected ensures that appropriate care is administered in acute and outpatient settings.

We describe a case encountered at our hospital of a patient with a false-positive troponin I level elevation, which led to unneeded investigations and intervention. We determined the nature of the interference, through laboratory analysis, and suggest an approach to follow when false-positive detection of troponin-level elevation is suspected.

Case

A 28-year-old woman presented to the emergency department with the complaint of intermittent diffuse paresthesia. She described recurring episodes of “bugs crawling under my skin” involving her whole body, preferentially in her hands and feet, and lasting a few seconds. She denied chest pain, dyspnea, and palpitations. She did not report any other symptoms or recent viral illness. Two weeks prior to this visit, tamsulosin was prescribed by her primary care provider for flank pain.

Her medical history was notable for functional dyspepsia, anxiety, polycystic ovary syndrome, irritable bowel syndrome, and vitamin B12 deficiency. She did not take any medications apart from tamsulosin, 0.4 mg orally, daily. She had no known allergies, and she did not smoke or use illicit substances. Her family history was notable for coronary artery disease and hypertension.

On examination, her blood pressure was 145/90 mm Hg, and her heart rate was 117 beats per minute. Her other vital signs were normal. Her cardiovascular examination was notable for a flow

murmur across the precordium. The rest of the examination was unremarkable. An electrocardiogram was performed, which demonstrated normal sinus rhythm at a rate of 68 beats per minute and borderline nonspecific ST-T abnormalities (Fig. 1).

The complete blood count, and electrolyte, glucose, creatinine, vitamin B12, folate, ferritin, and thyroid-stimulating hormone levels were within normal limits. Her high-sensitivity troponin I (hsTnI) level (Abbott ARCHITECT STAT high-sensitive troponin-I, Chicago, IL) was reported as 10,111 ng/L (overall 99th percentile 30 ng/L, with female sex-specific 99th percentile reported as 16 ng/L), whereas her creatine kinase (CK) level was within the reference interval. Given the large hsTnI concentration, cardiology was consulted. The hsTnI reading was repeated 4 hours later and was 8776 ng/L. A bedside echocardiogram was normal.

Although a false-positive elevation was suspected, further investigations were performed to exclude other life-threatening causes for troponin elevation, as alternative assays were not immediately available at our hospital. The patient was admitted under telemetry for observation; acetylsalicylic acid 81 mg orally, daily and metoprolol 50 mg orally, twice daily, were initiated. Internal medicine and neurology consultations were obtained. A formal echocardiogram performed the next day was normal. A computed tomography scan of the chest and abdomen ruled out aortic dissection and pulmonary embolism. A cardiac computed tomography angiogram demonstrated normal coronary anatomy and a calcium score of zero. Brain and spine magnetic resonance imaging demonstrated nonspecific findings relating to the white matter in both cerebral hemispheres, and a questionable increase of T2 signal in the lower aspect of the thoracic spinal cord.

The hsTnI reading was repeated on day 2 (8877 ng/L) and on day 3 (9292 ng/L), with all results within 15% of the initial hsTnI concentration. Tests for rheumatoid factor, antinuclear antibody, anti-DNA, extractable nuclear antigen antibodies, and antineutrophilic cytoplasmic autoantibodies were negative. Telemetry did not reveal any findings, and she was asymptomatic throughout admission. Results of cardiac magnetic resonance imaging performed during admission were normal. Her blood sample was sent to another hospital where an alternate cardiac troponin I (cTnI) assay (Siemens

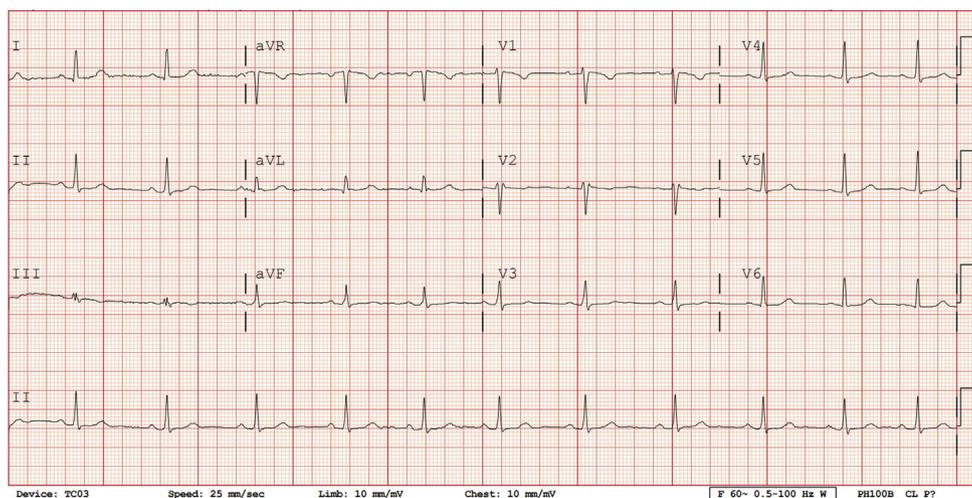


Figure 1. Electrocardiogram performed in the emergency department demonstrating nonspecific ST-T abnormalities.

Table 1. Troponin I (Abbott and Ortho Clinical Diagnostics) and Troponin T (Roche) levels measured in plasma and serum (ng/L)

Biomarker (manufacturer)	Treatment	Lithium heparin	% recovery	Serum	% recovery
TnI (Abbott)	Neat	1884	ND	1728	ND
	PEG precipitation	< 1	0	< 1	0
	Protein A/G pulldown	58	3	64	4
TnI (Ortho)	Neat	< 3	ND	< 3	ND
TnT (Roche)	Neat	< 1	ND	< 1	ND

Testing with the Abbott assay was repeated after post-polyethylene glycol (PEG) precipitation and protein A/G pulldown were performed.

Abbott, Abbott Laboratories (Chicago, IL); ND, not determined; Ortho, Ortho Clinical Diagnostics (Raritan, NJ); Roche, Roche Diagnostics (Indianapolis, IN); TnI, Troponin I; TnT, Troponin T.

Dimension Vista, a non-hsTnI assay; Munich, Germany) was performed, which yielded an undetectable cTnI level (cTnI < 15 ng/L, with upper 99th percentile of 45 ng/L). This result suggested false detection of an elevated hsTnI level, and in conjunction with the clinical workup, the patient was discharged on day 4 of admission, with no further acute follow-up and with medications discontinued. Two years later, no cardiovascular symptoms or events had been recorded; however, her hsTnI level, as measured by the Abbott ARCHITECT hsTnI assay, remained elevated, with a value of 1884 ng/L.

To determine the nature of the interference, on a research basis, we performed a series of experiments on specimens collected 2 years postdischarge. Repeat analysis showed the continued presence of elevated cTnI levels, by the Abbott assay (1884 ng/L and 1728 ng/L in plasma and serum, respectively). High-sensitivity cTnI (Ortho Clinical Diagnostics, Raritan, NJ) and high-sensitivity troponin T (Roche, Indianapolis, IN) assays produced undetectable cTnI and cardiac troponin T values. Post-polyethylene glycol precipitation, via Abbott hsTnI assay, also yielded undetectable results, confirming that the cause of the false elevation was a macrotroponin complex. Additional analysis using protein A/G immunodepletion demonstrated that the troponin macrocomplex is at least partially comprised of IgG, with a residual TnI level of < 5% (Table 1).

Discussion

In this report, we describe the case of a young female patient who presented with nonspecific noncardiac symptoms, but an electrocardiogram and a troponin assay were ordered. An hsTnI level of > 10 000 ng/L led to extensive investigation, as alternative assays for troponin were not immediately available. Repeat testing with an alternate troponin assay at another hospital yielded undetectable TnI levels 4 days into hospital admission. We suspected that our patient harboured a falsely elevated troponin level, likely due to macrotroponin complexes that interfered with the Abbott hsTnI assay.

Macrocomplexes consist of large immunoglobulin-troponin complexes with reduced clearance relative to non-complexed troponin. They may be associated with autoimmune disorders, although they are not believed to be disease-causing.⁴ Interference has been reported by assays produced by various manufacturers, including Abbott and Ortho Clinical Diagnostics.⁴ Reactivity to macrotroponin

varies among assays and may be more prevalent than once thought.^{3,4} The true incidence of macrotroponin is unknown; however, a few studies have suggested that it is relatively low, at 5% or less.^{3,4} However, the clinical impact can be significant, resulting in lengthened hospital stays, additional diagnostic testing, and unnecessary treatment.

Some approaches to address potentially analytical false-positive troponin results have been suggested.³⁻⁶ At minimum, clinicians should contact the laboratory medical (or technical) staff to initiate an investigation when troponin results are not consistent with the clinical picture. Investigations can include testing by an alternate method (ie, cTnI and/or cTnT) and by different methodologies, additional biomarkers with some cardio-specificity (eg, CK-MB isoform, heart-type fatty-acid binding protein, CK), use of human anti-mouse antibodies blocking agents in the case of human anti-mouse antibody interference, and post-polyethylene glycol precipitation when macrotroponin is suspected.

This case highlights the fact that patients may have macrocomplexes evident over the course of 2 years; thus, a process is needed to identify the presence of macrocomplexes for each encounter in which troponin is measured in these patients. A prudent measure is for hospitals to have a mechanism in place for the continued investigation of elevated troponin level results due to macrocomplexes, so that the most appropriate care is administered in acute and outpatient settings.

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Disclosures

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References

1. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *Eur Heart J* 2018;40:237-69.
2. Lum G, Solarz DE, Farney L. False positive cardiac troponin results in patients without acute myocardial infarction. *Lab Med* 2006;37:546-50.
3. Kavsak PA, Ainsworth C, Worster A. An approach to investigating discordant high-sensitivity cardiac troponin i results. *Can J Cardiol* 2021;37:1292-3.
4. Warner JV, Marshall GA. High incidence of macrotroponin I with a high-sensitivity troponin I assay. *Clin Chem Lab Med* 2016;54:1821-9.
5. Kavsak PA, Ainsworth C, Arnold DM, et al. The potential role of a turbidimetric heart-type fatty acid-binding protein assay to aid in the interpretation of persistently elevated, non-changing, cardiac troponin I concentrations. *Clin Biochem* 2018;58:53-9.
6. Saunders A, Tsui AKY, Alhulaimi N. Persistent troponin elevation in the setting of an elevated rheumatoid factor: when it pays to double check. *CJC Open* 2021;3:981-3.