

CASE REPORT

BEGINNER

CLINICAL CASE

Spuriously Elevated Cardiac Troponin in the Setting of Atypical Chest Pain Presentation



A Diagnostic Conundrum

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ABSTRACT

A 47-year-old woman presented with atypical chest pain and a troponin level of 30.15 ng/dL. A detailed diagnostic work-up did not detect an acute myocardial infarction but revealed the presence of heterophile antibodies. Laboratory values need to be interpreted in the context of the clinical picture when test results do not correspond to clinical findings.

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HISTORY OF PRESENTATION

A 47-year-old African American woman with a medical history of hypertension and nonobstructive coronary artery disease presented to the hospital with left-sided chest pain and a sensation of heaviness and numbness in her left arm that lasted for 12 h. She reported having experienced similar episodes of intermittent chest pain associated with left arm numbness over the previous 5 months. The pain was described as a stabbing sensation, lasting for a few

seconds to minutes and occurring both at rest and with activity. It was not associated with nausea, vomiting, or diaphoresis. Vital signs on admission revealed blood pressure of 170/92 mm Hg, heart rate of 65 beats/min, respiratory rate of 22 breaths/min, and oxygen saturation of 100% on room air. Physical examination, including a comprehensive cardiovascular examination, was unremarkable except for the presence of an apical S₄.

PAST MEDICAL HISTORY

The patient had presented in a similar fashion to an outside facility in Georgia 5 months before this presentation. At that time, she reportedly underwent left-sided heart catheterization (LHC) that showed nonobstructive coronary artery disease (~30% left circumflex lesion). She subsequently moved to our city and started working in a plasma donor center.

LEARNING OBJECTIVES

- To recognize the spurious causes of hypertroponinemia.
- To incorporate the clinical context when analyzing diagnostic data.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* [author instructions page](#).

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The patient ran out of her antihypertensive medications after moving to our area.

DIFFERENTIAL DIAGNOSIS

Her presentation was concerning for several possibilities, including acute coronary syndrome (ACS), acute aortic dissection, and acute pulmonary embolism. ACS was initially thought to be the most likely cause because her chest pain occurred at rest and was associated with left arm numbness.

INVESTIGATIONS

The initial work-up in the emergency department included a 12-lead electrocardiogram (ECG) (Figure 1), a complete metabolic panel, and a complete blood count; all were unremarkable. A serum troponin I level was drawn and was found to be elevated at a strikingly high 30.15 ng/dl (normal: <0.04 ng/dl). This was the conventional Access AccuTnI+3 troponin I assay (Beckman Coulter, Brea, California; referred to here as the Beckman assay) and not a high-sensitivity troponin assay. Additional biomarker test results included a creatine kinase (CK) level of 120 U/l (normal: 30 to 223 U/l) and a lactate dehydrogenase level of 205 IU/l (normal: 110 to 270 IU/l). The second troponin I value was 32.21 ng/dl, and the third was

31.52 ng/dl, which represented an insignificant change.

Despite the normal 12-lead ECG, the marked elevation of serum troponin made the diagnosis of ACS high on our differential diagnosis. Therefore, the patient underwent an urgent LHC, which revealed only tortuous coronary arteries, consistent with hypertensive heart disease with no evidence of significant coronary obstruction or dissection (Figure 2).

The unremarkable results of the LHC led to further evaluation for noncoronary causes of myocardial necrosis (Table 1). Chest computed tomography angiography excluded aortic aneurysm and dissection. However, it did show a trivial pericardial effusion. An echocardiogram revealed mild left ventricular hypertrophy and mild global hypokinesis with a left ventricular ejection fraction of ~45% to 50%, possibly resulting from myocarditis or hypertensive cardiomyopathy secondary to her longstanding uncontrolled hypertension. The working diagnosis at that point shifted toward myocarditis versus other rare causes of troponin elevation. On hospital day 5, she underwent an endomyocardial biopsy, which revealed normal histologic findings. Subsequently, cardiac magnetic resonance revealed

ABBREVIATIONS AND ACRONYMS

- ACS = acute coronary syndrome
- CK = creatine kinase
- cTn = cardiac troponin
- ECG = electrocardiogram
- HAMA = human antimurine antibody
- LHC = left-sided heart catheterization

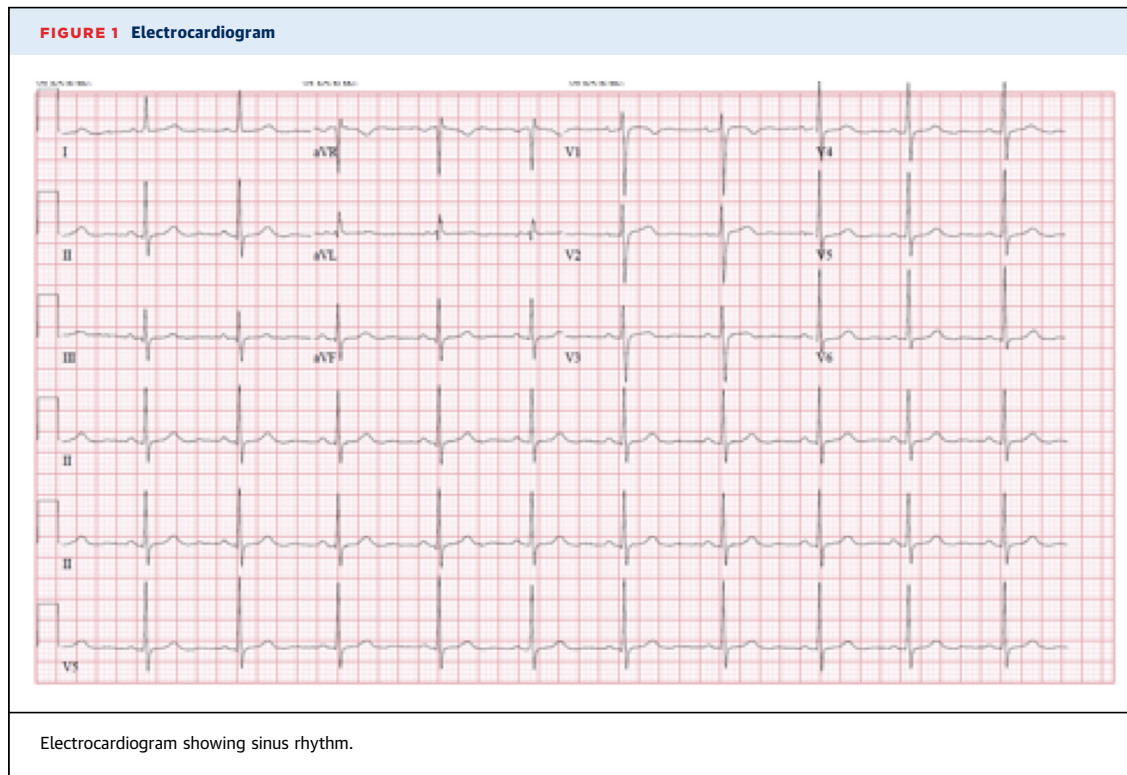
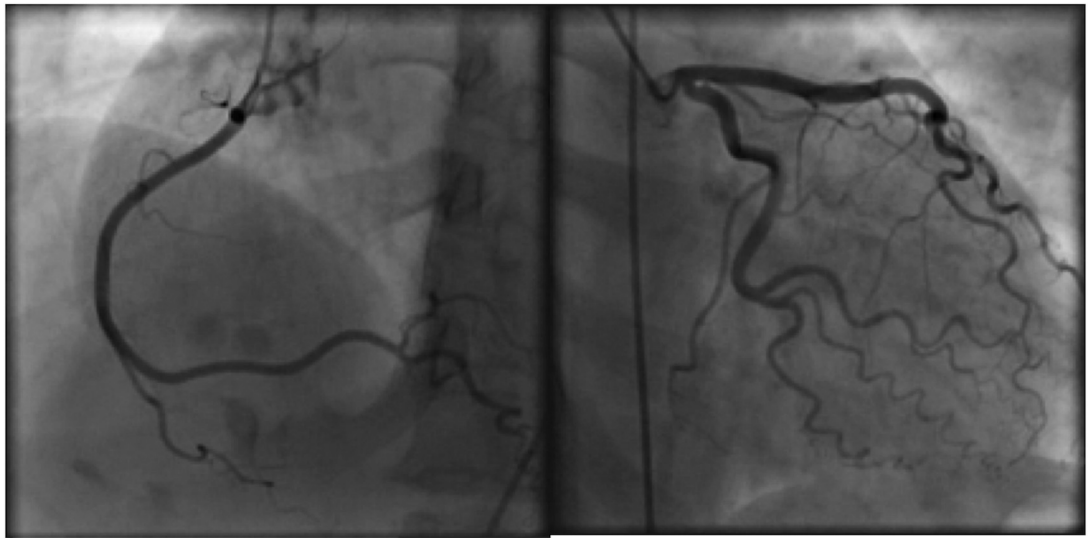


FIGURE 2 Cardiac Angiography

Left-sided heart catheterization showing no critical stenosis. The images show tortuosity of the left anterior descending artery, circumflex, and right coronary arteries.

low normal left ventricular systolic function with no regional wall motion abnormalities or findings to suggest inflammation or infiltration. There was a diffusion defect on the lateral side, likely representing microstructural anisotropy caused by myocyte hypertrophy, but no myocardial edema by T₂-weighted imaging (Figures 3A to 3D). Various other laboratory tests, including inflammatory markers and autoimmune serological examinations, were obtained (Table 2), but none initially yielded further diagnostic information.

At that point, an interfering substance with our facility's troponin I assay was suspected. We sent samples of troponin T and CK-MB for testing in an outside laboratory, but both were reported to be within normal limits. Meanwhile, we contacted the laboratory at the hospital in Georgia where the patient had initially presented with chest pain 5 months earlier. There, the troponin I value had been normal. We then aimed to investigate the type of troponin I used in our laboratory. Our facility uses the Beckman assay. The assay used for troponin I testing in Georgia was found to be the Architect i2000SR (Abbott, Abbott Park, Illinois; referred to here as Architect 2000). We located a nearby center where the Architect 2000 assay was also being used. We then rechecked troponin I at our facility and the outside laboratory using the same sample. Troponin I was found to be within normal range with the Architect 2000 assay at the outside laboratory and was markedly elevated, at 30 ng/dl, with the Beckman assay at our facility. Subsequent serological testing confirmed the presence of a human antimurine antibody (HAMA) that reacted with the murine antibody used in the Beckman troponin assay.

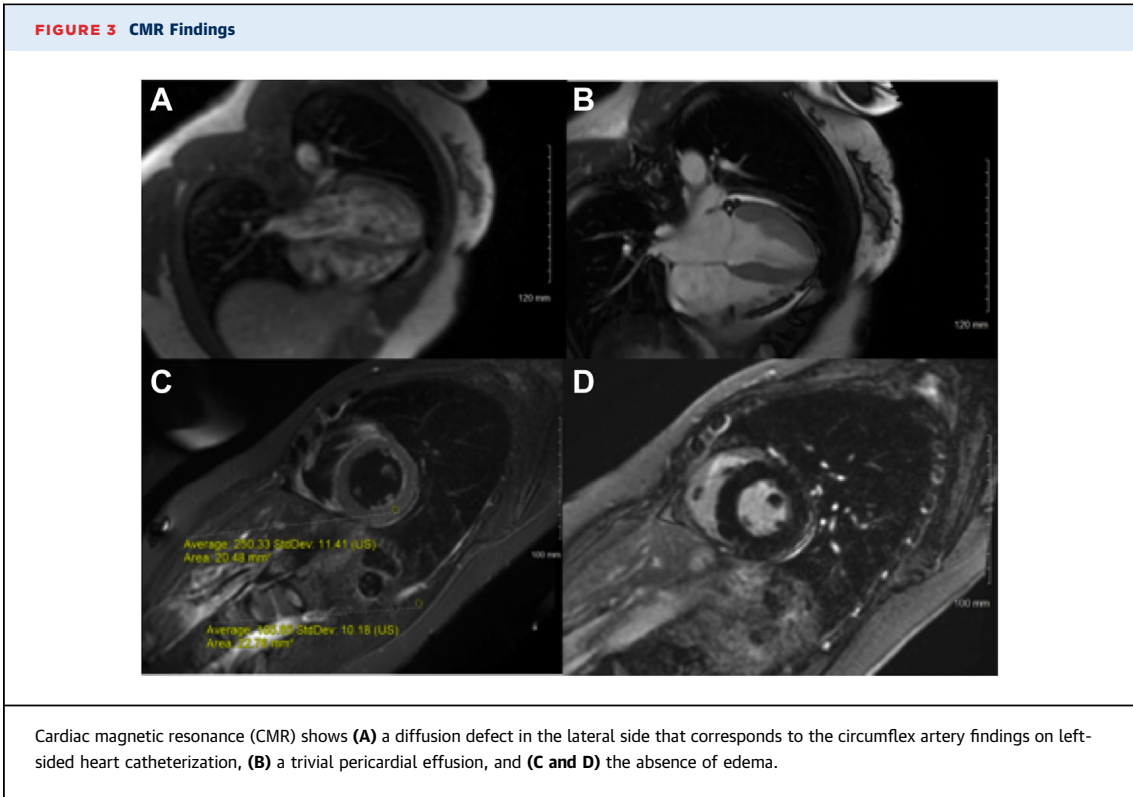
DISCUSSION

This case demonstrates an example of falsely elevated cardiac troponin (cTn) related to the presence of heterophile antibodies. Cardiac biomarkers

TABLE 1 Non-ACS and Noncardiac Causes of Troponinemia

Non-ACS Cardiac Causes of Elevated Troponin	Noncardiac Causes of Increased Troponin Levels
Acute and chronic heart failure	Renal failure
Myocarditis	Pulmonary embolism
Cardiac contusion from trauma	Severe pulmonary hypertension
Cardioversion	Sepsis
Endomyocardial biopsy	Severe critical illness
Aortic dissection	Burns
Hypertrophic cardiomyopathy	Extreme exertion
Aortic valve disease (aortic stenosis or regurgitation)	Acute stroke and subarachnoid hemorrhage
Cardiotoxic drugs	
Tachyarrhythmia (SVT, VT, atrial fibrillation)	
Bradyarrhythmia or heart block	
Cardiac surgery	
Cardioversion	
Takotsubo cardiomyopathy	
Rhabdomyolysis	
Stenting or angioplasty (percutaneous coronary intervention)	

ACS = acute coronary syndrome; SVT = supraventricular tachycardia; VT = ventricular tachycardia.



play a pivotal role in the diagnosis of myocardial injury and infarction, and their presence and degree of elevation have been associated with high rates of adverse cardiovascular outcomes in various clinical settings (1,2). Nonspecific biomarkers such as aspartate aminotransferase, lactate dehydrogenase, and CK were initially replaced by the more specific MB fraction of CK. However, on iterative revisions of the definition of myocardial infarction, it has become widely acceptable to use cTn as the biomarker of choice because of its higher sensitivity and tissue specificity. The Fourth Universal Definition of Myocardial Infarction (2018) proposed the following criteria (3,4): the term *acute myocardial infarction* should be used when there is clinical evidence of myocardial ischemia and detection of a rise and/or fall of cTn values above the 99th percentile upper reference limit with at least 1 of the following: 1) ischemic ECG changes; 2) development of Q waves; 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with ischemia; or 4) identification of a coronary thrombus by angiography or autopsy. Along with cTnI, we concomitantly measured the aforementioned biomarkers, and in retrospect, the normal level of CK-MB should have cast serious doubts about

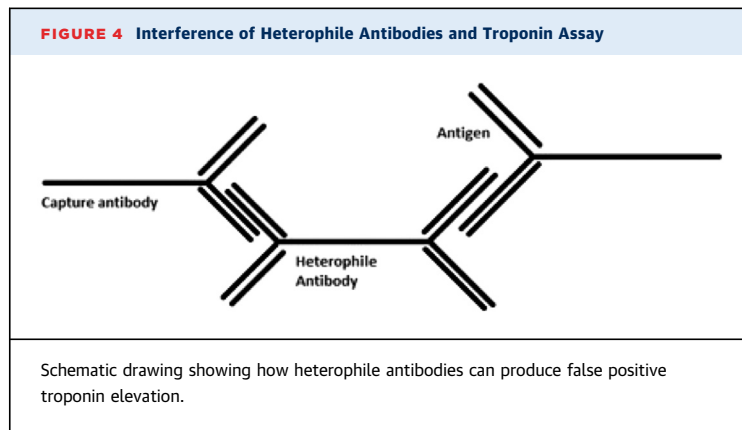
the validity of the elevated cTn and altered the course of our diagnostic work-up. The markedly elevated cTn prompted an urgent proceeding with cardiac catheterization, even before performing an echocardiogram. However, invasive procedures carry certain risks and should be reserved for cases with clear indications and appropriate use criteria.

It is not uncommon for patients with non-ST-segment elevation myocardial infarction to have normal ECGs or nonspecific ST-T change. An ischemia cascade typically begins with myocardial

TABLE 2 Laboratory Tests, Including Inflammatory Markers and Autoimmune Serological Examinations, in the Case Study

Test	Value
Creatine kinase	120 U/l
Lactate dehydrogenase	Negative
Sedimentation rate	3 mm/h
C-reactive protein	1.8 mg/l
Rheumatoid factor	<10.0 U/ml (negative)
Antinuclear antibody	Negative
TSH	0.33 mIU/l (normal)
HIV antibody	Negative
Hepatitis C antibody	Negative
D dimer	0.75 mg/l (positive)

HIV = human immunodeficiency virus; TSH = thyroid-stimulating hormone.



hypoperfusion, and cardiac biomarkers often rise in a gradual fashion, peaking around the first 24 to 48 h. However, there are several limitations to using cardiac biomarkers in clinical practice, including cases in which cTn can be elevated in non-ACS conditions. These are further divided into non-ACS cardiac and noncardiac causes (Table 1). Thus, the clinical diagnosis of acute myocardial infarction requires a comprehensive assessment of symptoms and ECG findings, in addition to the presence of cardiac biomarker abnormalities with a typical rise and fall pattern.

A scarcely reported problem is related to spuriously elevated cTn, which either can represent a technical issue with the development of commercially available assays or can signal the presence of interfering substances, including heterophilic and antianimal antibodies. The detection of cTn on such assays uses an immunoassay mechanism that is inherently subject to erroneous results in the presence of interfering antibodies. Troponin immunoassays often use a pair of monoclonal antibodies (capture and label antibodies) directed at 2 binding sites (sandwich) for troponin detection (Figure 4). The capture antibody initially binds to any troponin in the sample. The label antibody is added after a wash phase and binds to the captured troponin, thereby providing a quantifiable signal. The Beckman assay uses a pair of antibodies lying next to each other and directed against epitopes in the heart-specific and stable region of the troponin molecule close to the NH₂ terminus. The heterophile antibodies can form links with antibodies used in Beckman assays, thus mimicking the cTn antigen for which the assay was designed and giving rise to spuriously high troponin levels. Conversely, the Architect 2000 assay incorporates 1 antibody directed toward the heart-specific region close to the NH₂ terminus and

another antibody directed against epitopes in the stable part closer to the COOH terminus (5).

Detectable levels of heterophile antibodies can be associated with exposure to a variety of antigens, including the following: transfused blood components; vaccinations; viral infections such as cytomegalovirus, human immunodeficiency virus, and viral hepatitis; and even dietary antigens. Additionally, heterophile antibody activity has been observed in leukemia and rheumatoid arthritis. This is of particular importance because in some conditions the antibodies may be present only transiently in low levels, thus resulting in erroneous negative conclusions because of saturation of the assay antibody, or in very high levels, as in our case, resulting in falsely elevated values. The presence of such antibodies can otherwise be clinically silent, with an incidence ranging between 9% and 40% in the general population in some reports and anywhere from 1% to 80% in other series (6–8). HAMA is probably the most common antianimal antibody, and its presence can be iatrogenic (immunized after treatment or imaging with agents containing mouse antibody) or non-iatrogenic (8).

Heterophile antibody interference challenges most, if not all, cTn immunoassays. However, as in our case, antibodies that interfere with 1 assay may not affect another. The exact mechanism of such discordance remains elusive. Similar cases have been found in published reports, both for troponin elevation and for erroneous elevation of CK-MB, beta-human chorionic gonadotropin, thyroid-stimulating hormone, and carcinoembryonic antigen, all using the “sandwich” mechanism for detection of serum proteins (9,10). There are modern high-sensitivity assays that incorporate heterophilic antibody blocking tubes, thereby removing the antibody and reducing the chance of interference (11). However, some degrees of interference can still occur in these assays. Such tubes should be used in patients when the clinical picture does not correlate with the cTnI or cTnT elevation or when no cause for such elevation is obvious.

Notwithstanding the lack of evidence, we suspect that our patient’s exposure to blood products in the plasma donor center may have led to the development of HAMA antibodies.

FOLLOW-UP

In follow-up, the patient continued to report recurrent episodes of atypical left-sided chest and arm discomfort. She received a diagnosis of carpal tunnel syndrome and underwent tendon release surgery. On

one of her presentations, the cTnI level was checked and again was found to be extremely elevated at 143 ng/dl. Because there was no other evidence of myocardial infarction, this finding was attributed to her heterophile antibodies.

CONCLUSIONS

The clinician's suspicion remains key to the recognition of erroneous results, whereas laboratory confirmation should carefully be pursued in judicious ways. Ultimately, the diagnosis of falsely elevated cTn can be made on the basis of discordance between the clinical and laboratory findings (in our case, persistently elevated cTn against a background of nonspecific chest pain, nondiagnostic ECG, and lack of imaging and tissue evidence of myonecrosis and inflammation). In our case, we had to perform an extensive work-up because of a markedly, yet falsely,

elevated cTn level. Heuristically driven clinical decision making led to delayed recognition of an epiphenomenon and an unnecessary cascade of diagnostic testing. The main practical lesson learned here is that laboratory values should be interpreted within the framework of the clinical picture, to avoid unnecessary diagnostic testing and prolonged hospital stay.

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REFERENCES

1. Apple FS, Murakami MM, Pearce LA, et al. Predictive value of cardiac troponin I and T for subsequent death in end stage renal disease. *Circulation* 2002;106:2941-5.
2. Giannitsis E, Müller-Bardorff M, Kurowski V, et al. Independent prognostic value of cardiac troponin T in patients with confirmed pulmonary embolism. *Circulation* 2000;102:211-7.
3. Jaffe AS, Ravkilde J, Roberts R, et al. It's time for a change to a troponin standard. *Circulation* 2000;102:1216-20.
4. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol* 2018;72:2231-64.
5. James S, Flodin M, Johnston N, Lindahl B, Venge P. The antibody configurations of cardiac troponin I assays may determine their clinical performance. *Clin Chem* 2006;52:832-7.
6. Thompson RJ, Jackson AP, Langlois N. Circulating antibodies to mouse monoclonal immunoglobulins in normal subjects—incidence, species specificity, and effects on a two-site assay for creatine kinase-MB isoenzyme. *Clin Chem* 1986;32:476-81.
7. Boscato LM, Stuart MC. Incidence and specificity of interference in two-site immunoassays. *Clin Chem* 1986;32:1491-5.
8. Kricka LJ. Human anti-animal antibody interferences in immunological assays. *Clin Chem* 1999;45:942-56.
9. Primus FJ, Kelley EA, Hansen HJ, Goldenberg DM. "Sandwich"-type immunoassay of carcinoembryonic antigen in patients receiving murine monoclonal antibodies for diagnosis and therapy. *Clin Chem* 1988;34:261-4.
10. Mair J, Lindahl B, Müller C, et al. What to do when you question cardiac troponin values. *Eur Heart J Acute Cardiovasc Care* 2018;7:577-86.
11. Kim WJ, Laterza OF, Hock KG, et al. Performance of a revised cardiac troponin method that minimizes interference from heterophile antibodies. *Clin Chem* 2002;48:1028-34.

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