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CASE REPORT

False elevation of cardiac markers: importance of recognition

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Abstract: The availability of troponins as cardiac markers in the diagnosis of acute coronary syndrome is invaluable. However, their elevation can sometimes lead the physician astray. We report a rare case of an 86-year-old Hispanic female with a past medical history significant for asthma, hypertension, atrial fibrillation, and dyslipidemia, who presented to the emergency room complaining of a two-day history of shortness of breath associated with wheezing. She denied any chest pain. The patient's wheezing ameliorated with bronchodilator treatment. However, her admission laboratory investigations were positive for elevated troponin I, with normal creatine kinase (CK) and CK-myoglobin (MB). The first set of cardiac enzymes revealed a troponin I of 29.16 ng/mL (normal < 0.05 ng/mL), CK 234 IU/L, and CK-MB 3.9 IU/L. The electrocardiogram showed rate-controlled atrial fibrillation with nonspecific ST changes. Subsequent cardiac enzymes failed to show any increase in CK or CK-MB. However, the troponin I was, as on admission, persistently elevated at 20.87–29.16 ng/mL. Subsequent cardiac catheterization revealed mild nonobstructive coronary artery disease. Other laboratory tests showed normal creatinine, alkaline phosphatase, and bilirubin, and a negative rheumatoid factor, with absence of hemolysis. A blood sample was subsequently drawn and sent to Beckman Coulter laboratories for heterophile antibody testing. The results confirmed our suspicion of a falsely elevated troponin I caused by the presence of a heterophile antibody. The addition of blocking agents yielded troponin I levels in the normal range. Consistent with current guidelines, we conclude that cardiac markers should be used in conjunction with the clinical picture and the electrocardiogram. This case is unique in that the troponin elevation was incidentally found and led to an array of tests which were all negative.

Keywords: troponin I, antibodies, coronary syndrome, electrocardiogram

Background

Traditional methods of diagnosing acute coronary syndrome rely on the patient's history, physical examination, an electrocardiogram, and cardiac markers. This case is interesting in that the patient presented with shortness of breath and was found to have a troponin I of 26.6 ng/mL. A subsequent lengthy invasive work-up was negative for any cause of elevated troponins. After exhausting all other causes of elevated troponins, we found the presence of a heterophile antibody. We report the presentation, workup, and outcome of this rare case, and review the relevant literature.

Case presentation

An 86-year-old Hispanic female with a past medical history significant for asthma, hypertension, atrial fibrillation, and dyslipidemia presented to the emergency room

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complaining of a two-day history of worsening shortness of breath associated with wheezing. She denied any chest pain, palpitations, or diaphoresis. She was on medications of enalapril, simvastatin, warfarin, diltiazem, and albuterol. She denied any recent change in her medication regimen and stated that she had not taken any new medications. The patient's wheezing ameliorated with bronchodilator treatment administered in the emergency room.

Admission laboratory measurements were positive for elevated troponin I, with normal BNP, creatine kinase (CK) and CK-myoglobin (MB). The first set of cardiac enzymes revealed troponin I of 26.6 ng/mL, CK of 234 IU/L, and a CK-MB of 3.9 IU/L. Subsequent cardiac enzymes failed to show any increase in CK or CK-MB. However, the troponin I, as on admission, was persistently elevated at 20.87–29.16 ng/mL. The patient's electrocardiogram showed rate-controlled atrial fibrillation at 70 beats per minute with nonspecific ST changes, which were present on a previous electrocardiogram. The chest x-ray was unremarkable, without any evidence of heart failure or infiltrates. Review of her past and current medical history failed to account for the abnormal elevation in troponin I levels. An echocardiogram was performed, which showed an ejection fraction of 50%–55%, with inferior wall hypokinesia, and there was evidence of trace mitral regurgitation without any evidence of vegetations or pericardial effusion. Due to the elevated cardiac markers and inferior wall hypokinesia, cardiac catheterization was subsequently performed, which revealed mild nonobstructive coronary artery disease. The right coronary artery was normal, the left main was free of disease, the mid circumflex had a 20% lesion, and the left anterior descending was free of disease angiographically.

Of importance were the results for other laboratory parameters accounting for elevated troponins, which were found to be negative or within the normal range, ie, creatinine, alkaline phosphatase, bilirubin, rheumatoid factor, and hemolysis. Furthermore, her electrocardiogram did not show any evidence of ischemic changes. A diagnosis of falsely elevated troponins was suspected, with hypothesized presence of a heterophile antibody. A blood sample was subsequently drawn and sent to Beckman Coulter laboratories for heterophile antibody testing. The results confirmed our suspicion of falsely elevated troponin I levels caused by the presence of a heterophile antibody. The addition of blocking agents yielded troponin I levels in the normal range. Consistent with the current literature, we conclude that cardiac enzymes should be used in conjunction with the clinical picture and the electrocardiogram.

Discussion

Despite the high specificity of cardiac troponins, this case report shows that they can be misleading. Our case is unique in that the patient underwent multiple tests, in addition to cardiac catheterization, all of which did not explain the elevated troponin level. Furthermore, a review of the literature on published heterophile antibody cases shows that troponin I is minimally elevated, unlike in our patient who had a troponin I of 29.16 ng/mL. Moreover, the troponin I increased from 26.6 to 29.16 ng/mL within six hours of admission. This rise further raised our suspicion of the presence of coronary artery disease.

Cardiac troponins I and T are regulatory cardiac proteins that control calcium-mediated interaction of actin and myosin.[1] Specific genes code for these proteins and thus, their cardiac form makes them unique to the heart. Studies performed with cardiac troponin I have failed to find any cardiac troponin I outside of the heart at any stage of neonatal development.[2,3] In contrast, cardiac troponin T is expressed to a minor extent in skeletal muscle. However, the present cardiac troponin T assay does not detect these forms.[4] Because of their increased specificity compared with CK-MB and other markers, troponins are the preferred marker for the diagnosis of myocardial injury.[5–7] The use of cardiac troponin I or cardiac troponin T for the diagnosis of myocardial infarction was recommended by a consensus statement of the European Society of Cardiology and the American College of Cardiology in 2000, and by a task force of the American College of Cardiology and the American Heart Association in 2004.[5,7] The skeletal and cardiac isoforms of troponin T and troponin I are distinct, and skeletal isoforms are not detected by the monoclonal antibody-based assays currently in use.[8] The clinical utility of troponins I and T is attributed to their specificity for cardiac muscle. Contemporary troponin assays are extremely sensitive and can detect very small amounts of myocardial necrosis (<1 g). International consensus committees have established that an elevated value for cardiac troponin be defined as a value exceeding the 99th percentile of a reference control group and that imprecision be defined as a coefficient of variation of $\leq 10\%$.[15]

If the patient's clinical picture for acute myocardial infarction or acute coronary syndrome do not match an elevated troponin result, the laboratory should suspect a false-positive troponin value caused by analytical interferences with this assay. These interferences are summarized in Table 1.[9] A false-positive troponin result is a reminder that, although troponin plays an important role in the diagnosis of acute myocardial infarction and acute coronary syndrome, it should not be the

Table 1 Factors that falsely elevate troponin I

Fibrin clots
Microparticles in sample
Heterophile and human antianimal antibodies
Bilirubin
Hemolysis
Lipemia
Elevated alkaline phosphatase
Macroimmunocomplex formation
Analyzer malfunction
Rheumatoid factor

only criterion for establishing these diagnoses. A variety of clinical conditions other than myocardial infarction may be associated with elevated cardiac troponin levels (Table 2).[10–12] Furthermore, elevated troponins are reported in Takotsubo cardiomyopathy,[13] in which there is reversible left ventricular dysfunction associated with emotional stress, with evidence of exaggerated sympathetic activation.[13]

As such, in August 2005, the Office of In Vitro Diagnostic Device Evaluation and Safety of the United States Food and Drug Administration, using input provided by the Advanced Medical Technology Association, issued an advisory regarding false elevations in cardiac troponin results in response to many manufacturers' and users' reports of false-positive troponin levels and on the basis of articles in the medical literature.[14] The purpose of the advisory was to inform laboratories about the possibility of false-positive troponin values when this marker is used in the diagnosis of acute myocardial infarction, and to recommend steps to be followed by the laboratory to identify and confirm cases of a false-positive troponin result.[14]

As already mentioned, one vector that yields a false-positive troponin level is the presence of a heterophile antibody in the patient's serum. Heterophile antibodies are produced against poorly defined antigens, and are generally weak antibodies with multispecific activities.[16] Heterophile antibody is a term used interchangeably to refer to human antianimal antibodies, rheumatoid factor, and other autoantibodies.[17] Human antianimal antibodies are antibodies with strong avidities, are produced against well-defined antigens, and develop as a result of treatment or exposure to animal immunoglobulins.[18] Circulating human antianimal antibodies may have specificities for a wide range of animal proteins, such as mouse, rabbit, rat, and others.[18] Circulating heterophile and human antianimal antibodies may have iatrogenic and noniatrogenic causes, including blood transfusions, vaccination against infectious diseases, exposure to microbial antigens, use of mouse monoclonal antibodies for therapeutic and imaging purposes, animal husbandry or keeping of animals as pets, transfer of dietary antigens across the gut wall in celiac disease, and autoimmune diseases that may give rise to autoantibodies, such as rheumatoid factor.[18]

Table 2 Clinical situations in which the troponin I can be elevated

Acute pulmonary embolism
Myocarditis
Acute pericarditis
Cerebrovascular accidents
Hypovolemia
Heart failure
Sepsis/critically ill
Renal failure
Tachyarrythmias
Myocardial contusion

Immunoassays for cardiac troponin I often employ two-site (sandwich) or competitive reactions which contain two antibodies specific at two sites for the measured analyte.[9] The first antibody, ie, the "capture" antibody, initially binds to any cardiac troponin I in the sample. The second antibody, ie, the "label" antibody, is then added after a wash phase and binds to any "captured" cardiac troponin I, providing a detectable signal that can be measured to quantify the cardiac troponin I concentration after a final wash phase.[9] Human antianimal and heterophile antibodies, which are specific for the F_c portion of the assay species, immunoglobulin, and may crosslink, capture, or label antibodies in the absence of the intended analyte, may cause a positive assay response.[19] Because of this potential interference, manufacturers generally add nonspecific blocking antibodies of the assay species, which are intended to limit the effect of any heterophile antibodies present in the sample. However, in some cases, when sufficient quantities of interfering antibodies are present, analytical errors may occur.[9]

The prevalence of antianimal and antimouse antibodies is unknown, and estimates vary widely from $<1\%$ to 80%.[18] A commonly cited prevalence of 40% for heterophile antibodies for interference in two-site immunoassays was found in 1986 for 188 subjects.[20] The laboratory can use multiple modalities to reduce or remove the effect of interfering antibodies from troponin assays, and these are summarized in Table 3.[9]

Table 3 Factors to minimize interference by heterophile antibodies

Specimen can be analyzed on a different manufacturer's assay system
Heterophile blocking reagents can be used
Add endogenous immunoglobulin-free serum samples to the specimen to remove endogenous immunoglobulins

Conclusion

The diagnosis of acute coronary syndrome relies on history, electrocardiogram, and cardiac markers. Cardiac markers are very helpful in aiding physicians to diagnose coronary artery disease. Physicians should be aware that these laboratory values can be invaluable when used appropriately, but should be used in conjunction with clinical and electrocardiographic findings. The case described here underscores the importance of recognizing falsely elevated cardiac markers in the absence of any pathology.

Disclosure

The authors report no conflicts of interest in this work.

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