CASE REPORT

A non-ischaemic cause of elevated troponin

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SUMMARY

A 27-year-old woman with chest pain was admitted for elevated troponin levels. Troponin remained mildly elevated upon repeat testing, and a review of the medical record revealed that she had had an elevated troponin level in the past. She had a cardiac catheterisation that revealed angiographically normal coronary arteries. Repeat troponin testing with and without ethylene glycol revealed a negative troponin level after addition of ethylene glycol, suggesting antibodies were interfering with the assay.

BACKGROUND

Cardiac troponins are proteins involved in regulating the contraction of cardiac muscles. Cardiac troponins can be used as biomarkers for myocardial necrosis and aid in the diagnosis of thrombotic acute coronary syndromes.¹ In 2000, a consensus statement was released by the Joint European Society of Cardiology/American College of Cardiology Committee, stating that cardiac troponin was the preferred biomarker for myocardial damage. The committee noted that cardiac troponin has 'nearly absolute myocardial tissue specificity'.¹ However, in a more recent consensus statement, it was clarified that 'an elevated troponin is a finding that represents the likely occurrence of myocardial necrosis and does not in and of itself provide any indication of the aetiology'.² Elevations may be indicative of a variety of non-coronary disorders such as sepsis, renal failure, pulmonary embolism, hypotension, pericarditis and congestive heart failure.³ Also of note, false-positive results may be caused by antianimal 'heterophile' antibodies, antitroponin antibodies, fibrin clots,^{4 5} microparticles, analyser malfunction or rheumatoid factors.⁵ It is estimated that heterophilic antibodies interfere with assays in 2.0% of cases.⁶

This case demonstrates the importance of recognising falsely elevated troponin levels. In the current case, the patient ultimately underwent invasive cardiovascular testing. Such invasive measures could have been avoided with appropriate recognition of and testing for heterophile antibodies.

CASE PRESENTATION

A 27-year-old woman presented to the emergency department with substernal chest tightness. She noted that the tightness had been intermittent, lasting between 15 min and 2 h per episode and occurring mainly at night. She noticed no correlation with activity. She reported no radiation of the tightness, nausea, vomiting or shortness of breath.

Her review of systems was positive for palpitations and diaphoresis.

She had two previous admissions in the prior year for similar symptoms and elevated troponin. She had been treated symptomatically with nitroglycerin and morphine during those admissions, and when troponin levels did not rise, she was discharged to follow-up with cardiology. However, she had not been compliant with the follow-up. She had a medical history of anxiety and gastro-oesophageal reflux disease (GERD). She denied alcohol and drug use, but admitted to smoking half a pack of cigarettes per day. She reported no family history of coronary artery disease.

INVESTIGATIONS

During the current admission, the patient had an investigation for ischaemic chest pain performed in the emergency department. Her ECG showed no ischaemic changes and was unchanged from an ECG performed during a prior hospital admission. The troponin returned elevated at 0.25 ng/mL (normal <0.05 ng/mL) with a normal CK and CKMB.

The patient was admitted to the hospital and monitored on telemetry. Her symptoms improved with nitroglycerin and morphine. She had repeat troponins at 6 and 12 h, which were 0.23 and 0.24 ng/mL, respectively. During the previous two admissions, the patient had elevated troponins that remained stable.

DIFFERENTIAL DIAGNOSIS

Initial differential diagnoses included cardiac versus non-cardiac origins of chest pain. Non-cardiac chest pain (NCCP) is recurrent angina-like pain in the absence of evidence of coronary heart disease on angiography or troponin assay.⁷ Clinically, it is difficult to distinguish NCCP from cardiac-related chest pain.^{8 9} In this case, the patient's elevated troponins was suspicious of a cardiac origin of chest pain. However, she also reported a history of GERD and anxiety, which are both strongly associated with NCCP.^{7 10 11}

While not wholly understood, potential mechanisms for chest pain resulting from GERD include oesophageal hypersensitivity or sustained contractions of the oesophageal longitudinal muscle.⁸ In a recent meta-analysis, Wertli *et al*¹² have reported that high-dose proton pump inhibitor treatment is an efficient diagnostic approach for GERD in the context of NCCP. GERD should be considered highly likely if treatment response occurs within 1 week but highly unlikely if there is no response after 4 weeks. Other tests used to confirm a

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diagnosis of GERD include ambulatory 24 h oesophageal pH testing and upper gastrointestinal endoscopy.

Psychiatric disorders are a common non-GERD-related cause of NCCP. A large percentage of patients with NCCP have been diagnosed with psychiatric comorbidities, most frequently anxiety, panic disorder or major depression.⁸ Psychiatric conditions are associated with physiological symptoms (eg, lightheadedness, dizziness, faintness or diaphoresis)¹² that may initiate ED presentation for NCCP. In addition, psychological symptoms of anxiety such as worry, tension and feeling frightened are associated with NCCP.¹¹ Screening measures in the ED may enable physicians to either rule out psychiatric disorders or refer patients for further assessment of symptoms and their potential relationship to NCCP.¹²

TREATMENT

While in the hospital, the patient was continued on aspirin and given nitroglycerin and morphine as needed for pain. She was discharged home with ativan, nexium and aspirin.

OUTCOME AND FOLLOW-UP

The patient was discharged and scheduled for an outpatient catheterisation. She underwent cardiac catheterisation 2 weeks later, which revealed angiographically normal coronary arteries. Given her normal workup, falsely elevated troponins were suspected. A troponin assay was then ordered with and without the addition of ethylene glycol, which showed levels of <0.05 ng/mL and 0.21 ng/mL, respectively.

After receiving the test results, the patient was informed that her chest pain was of non-cardiac origin and was most likely associated with her symptoms of GERD and anxiety. She was referred to gastroenterology and psychology for follow-up and further assessment of her symptoms of GERD and anxiety, respectively. However, she was not compliant with the follow-up.

DISCUSSION

Troponin assays consist of two proteins, a capture protein and an immunofluorescent protein.¹³ The capture protein links troponin to the immunofluorescent protein, and analysers determine the amount of troponin in a sample based on the amount of light that is fluoresced.¹³ Heterophile antibodies interfere with troponin assays by binding to a portion of the assay, giving a false indication of elevated troponins.

The estimated prevalence of heterophilic antibodies varies greatly, ranging from a reported 0.17–40%.⁵ Individuals may acquire antianimal antibodies by exposure to the animal.¹⁴ However, individuals may be exposed to these antigens by diagnostic or pharmaceutical agents, blood transfusion or vaccination. In addition, antigens may be transferred across the placenta from mother to baby, may be caused by exposure to microbial antigens, autoimmune diseases or exposure may occur during digestion in certain conditions. Many previously published case reports indicate an inability to determine exposure to antigens, as the individuals had not had recent exposure to blood transfusion, imaging or any other known exposures that could account for heterophilic antibodies.^{15–17} In the current case, the patient had not had any of the aforementioned risk factors.

Some analysers use reagents that contain animal antibodies that block common human antianimal antibodies in the patient's serum. In addition, interference due to heterophile antibodies can be counteracted in several ways. A patient's blood may be diluted with animal serum, which allows actual cardiac troponin

levels to be measured.¹⁷ Alternatively, using an immobilised protein column A to run the patient's plasma can remove substances that interfere with true readings.¹⁷ As in the current case, precipitating the sample in polyethylene glycol can result in more accurate readings. Several case reports indicate that using a different analyser can easily indicate false positives.^{6 18–20}

There are a number of case reports in the literature that illustrate the importance of detecting falsely positive troponin levels.^{13 15–25} As in the current case, a number of patients underwent hospital admission and, in some instances, invasive testing due to delayed realisation that the test was a false positive.^{16–18 21 22 24 25} Alternatively, there are several case reports in which the treating physician suspected false-positive test results in a timely manner, avoiding unnecessary admissions and hospitalisations.^{15 19 20 23}

In a recent consensus document, Newby *et al*² point out that troponin testing is one element of assessment of global risk, and ideally, would be used in a clinically driven management algorithm. They offered an example, where patients would be stratified by high troponin levels and the presence or absence of a high pretest probability of an acute coronary syndrome. In their model, pretest probability was determined by presenting symptoms and history of risk factors. For individuals with elevated troponins and a low pretest probability, the authors recommend that the goal should be to identify the cause of the elevated troponin level. In another recent consensus document regarding the definition of myocardial infarction, Thygesen *et al*²⁶ recommend a rising and/or falling pattern of cardiac troponins in order to determine whether the elevations are acute or chronic. However, the authors state that the patient's pretest probability and timing of presentation be considered when no variations are present.

In conclusion, the current case presents a patient with a low risk of cardiac ischaemia. The patient had a history significant for anxiety and GERD and was being treated pharmacologically for both. Gastrointestinal diseases and psychological disorders are two of the leading causes of non-cardiovascular chest pain.¹² Given the patient's very low pretroponin risk profile, these non-cardiovascular causes of chest pain should have been further investigated and cardiac disease should have been much lower on the differential. Using guidelines^{2 26} such as low pretest probability and absence of a rising or falling pattern of troponins may have resulted in the identification of falsely elevated troponins prior to invasive testing. However, failure to recognise falsely elevated troponins led to hospital admission and additional invasive testing.

Learning points

- ▶ Not all positive troponins are due to cardiac ischaemia.
- ▶ A mildly elevated troponin level that does not rise or return to baseline levels should raise suspicion of an error with the assay.
- ▶ History, physical, ECG and risk stratification should be considered when making the diagnosis of cardiac ischaemia.

Competing interests None.

Patient consent Obtained.

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