Learning from errors

False positive cardiac troponin elevation due to heterophile antibodies: more common than we recognise?

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Summary

A 53-year-old woman was admitted with non-exertional chest pain and elevated cardiac troponin I (cTnI) without dynamic changes of ischaemia on the ECG. She had recently undergone coronary angiography which had shown normal coronary vessels. Repeat angiography on this admission was again unremarkable. Samples of blood were sent for analysis using different troponin assays and demonstrated chronic basal elevation of cTnI while simultaneous assay for troponin T (cTnT) remained normal. Subsequent testing revealed the presence of heterophile antibodies interfering with the troponin I assay leading to a false positive result.

BACKGROUND

This case demonstrates an example of false positive cardiac troponin elevation due to the presence of heterophile antibodies. Although the prevalence of such interference with troponin assays is unknown, we have seen two such cases in recent months in our cardiac unit. It seems likely that many more cases like this go undetected, and may lead to unnecessary and potentially harmful investigations and treatments. Various strategies exist to avoid this problem. In addition, it should be remembered that the diagnosis of acute coronary syndromes relies on accurate clinical history and interpretation of the ECG and should not be made on the basis of biomarkers alone.

CASE PRESENTATION

A 53-year-old woman was admitted with non-exertional chest tightness radiating to the left arm. She had a past medical history of depression and hypertension but had no other vascular risk factors. She had had two previous admissions over the past 12 months with similar pains associated with low level elevations of cardiac troponin I (cTnI). Clinical examination was unremarkable. Angiography 1 year previously had demonstrated normal coronary arteries.

INVESTIGATIONS

Her ECG showed minor fixed T-wave changes in the anterior leads. Peak cTnI was elevated at 0.37 (normal 0–0.069). Echocardiography showed no abnormality.

TREATMENT

She was treated as having a troponin-positive non-ST elevation acute coronary syndrome. Anti-ischaemic and secondary preventive therapy was optimised. On the 5th day of her admission an exercise tolerance test was performed. This was deemed low risk and she was therefore discharged home.

OUTCOME AND FOLLOW-UP

An outpatient myocardial perfusion scan was arranged. This showed a small reversible perfusion defect in the territory of the left anterior descending artery. She underwent further coronary angiography which again demonstrated normal coronary arteries.

We subsequently took blood samples from the patient when she was seen in the outpatient department and was asymptomatic. Simultaneous blood samples were sent for measurement of cTnI in our own laboratory and for cardiac troponin T (cTnT) in a different laboratory. This showed that cTnI was chronically elevated, while simultaneous cTnT was normal.

It was therefore demonstrated that the raised cTnI was a false positive result. Further analysis revealed the presence of heterophile antibodies in the patient's blood, causing interference with our cTnI assay.

DISCUSSION

Cardiac troponins are single chain polypeptides involved in the regulation of cardiac muscle contraction. They are the most sensitive and specific markers of cardiac myocyte damage and are recommended for use in the diagnosis of acute coronary syndromes.¹ While only one assay for cTnT is commercially available, there are many different assays for cTnI in use.

Cardiac troponin elevation in the correct clinical context may confirm the diagnosis of acute coronary syndromes, and can also be used to stratify the risk of further adverse cardiac events. Elevated troponin levels may also result from a variety of non-coronary causes of cardiac myocyte necrosis (table 1). In addition, analytical errors may lead to false positive troponin elevations in the absence of myocyte necrosis. These errors may be related to interference with the troponin assay by fibrin,² alkaline phosphatase,³ haemolysis⁴ and instrumentation malfunction.

Table 1 Non-coronary causes of troponin elevation

Non-coronary myocyte necrosis*

- ▶ Acute severe cardiac failure
- ▶ Cardiac contusion
- ▶ Cardiac surgery
- ▶ Critical illness
- ▶ Pericarditis
- ▶ Pulmonary embolism
- ▶ Radiofrequency ablation
- ▶ Renal failure
- ▶ Sepsis
- ▶ Subarachnoid haemorrhage
- ▶ Supraventricular tachycardia

False positive†

- ▶ Alkaline phosphatase interference
- ▶ Fibrin interference
- ▶ Haemolysis
- ▶ Heterophile antibody interference
- ▶ Instrumentation malfunction
- ▶ Laboratory error
- ▶ Renal failure

* Non-coronary causes of cardiac myocyte necrosis and troponin elevation.

† Causes of troponin elevation in the absence of myocyte necrosis, that is, 'false positive' results.

The presence of heterophile antibodies in the serum of the test subject may also lead to a false positive result. These are defined as antibodies with multispecific activity produced against poorly defined antigens. Troponin assays are based on the principle of the two-site ELISA. Heterophile antibodies may bind non-specifically to the Fc-portions of the assay antibodies resulting in spurious troponin elevation.

Heterophile antibody production may be stimulated by exposure to a variety of antigens including transfused blood,⁵ vaccinations,⁶ exposure to mice⁷ and rabbits,⁸ therapeutic use of mouse monoclonal antibodies,⁹ and even dietary antigens.¹⁰ Autoimmune diseases may also give rise to antibodies with heterophile activity, for example, rheumatoid factor.¹¹

The precise prevalence of heterophile antibodies is unknown, and their interference with troponin assays has traditionally been considered to be rare. However, the prevalence of false positive troponin elevations in routine populations has been found in studies to be as high as 3.1%,¹² a proportion of which will be due to the presence of heterophile antibodies. One study of troponin elevations in rheumatoid factor positive subjects demonstrated 11.5% to be false positive results.¹³

A number of strategies exist to counteract interference from heterophile antibodies. Pooled animal sera may be used to remove anti-animal antibodies, and heterophile blocking agents are available and are incorporated into many of the newer assays.¹⁴ Blood may be sent for testing using a different assay on a simultaneous sample. Furthermore, serial samples should be sent in suspected acute coronary syndromes to look for a sequential rise and fall of cardiac biomarkers.

This case demonstrates an example of false positive cardiac troponin elevation due to the presence of heterophile antibodies. Although the prevalence of such interference with troponin assays is unknown, we have seen two such cases in recent months in our cardiac unit. It seems probable that many more cases like this go undetected, and may lead to unnecessary and potentially harmful investigations and treatments. Various strategies exist to avoid this problem. In addition it should be remembered that the diagnosis of acute coronary syndromes relies on accurate clinical history and interpretation of the ECG and should not be made on the basis of biomarkers alone.

Learning points

- ▶ Troponin is released from damaged cardiac muscle as a result of acute coronary syndromes or other non-coronary causes of cardiac myocyte necrosis.
- ▶ False positive results can occur in the absence of cardiac muscle damage, and may be due to the presence of heterophile antibodies.
- ▶ Various strategies exist to avoid heterophile antibody interference with troponin assays.
- ▶ Diagnosis of acute coronary syndromes must be made within the correct clinical context and not on the basis of biomarkers alone.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Zaidi A, Cowell R. False positive cardiac troponin elevation due to heterophile antibodies: more common than we recognise?. *BMJ Case Reports* 2010; 10.1136/bcr.11.2009.2477, date of publication

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