CASE REPORT

An unusually high troponin I result in association with *Legionella* infection

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SUMMARY

A 77-year-old man presented himself with shortness of breath that was initially felt to be due to an acute coronary event, largely due to a very elevated troponin I result and his medical history. He subsequently showed evidence to suggest a significant pneumonia. The most likely candidate organism responsible, from the history and test results, appeared to be *Legionella*. We present the case for a spuriously and extremely elevated troponin I result, being at least in part due the production of heterophil antibodies by *Legionella*.

BACKGROUND

Cardiac troponins I and T (cTnI and cTnT) are components of the myofibrillar contractile apparatus and are released into the circulation following cellular damage secondary to ischaemia, inflammation, trauma or toxins.¹ These markers are sensitive and usually specific to myocardial injury,² particularly troponin I, which has been shown to be 100% specific to the heart, while other isoforms are also raised in skeletal muscle injury.¹ Overall, they have become accepted markers in establishing a diagnosis of acute coronary syndrome and in determining the relevant course of action.

In the case of our patient, although a diagnosis of acute coronary syndrome was likely an alternative explanation contributing to an extremely elevated troponin I level, is proposed.

CASE PRESENTATION

A 76-year-old man presented himself with a sudden onset of difficulty in breathing, with a background of previous myocardial infarction. Coronary bypass surgery had been performed in 1978 and revised in 1988.

At 12 h postonset of symptoms, a troponin I level was recorded as >95 000 ng/L (normal range 0–40) and the patient was started on the acute coronary syndrome protocol.

He also reported a recent history of a productive cough and was started on oral co-amoxiclav for a lower respiratory tract infection.

Despite antibiotics, the temperature continued to spike and inflammatory markers (CRP) failed to improve, reaching a peak of 414 mg/L. On direct questioning, he described recent travel with hotel accommodations in Germany and Holland.

INVESTIGATIONS

The ECG showed sinus rhythm at 62 bpm, bifascicular block and widespread (longstanding) T-wave

inversion in the anterior (contributed to by the right bundle branch block) and high lateral leads.

Admission blood tests also revealed a raised white cell count of $11.6 \times 10^9/L$ (neutrophils elevated at $10.5 \times 10^9/L$, lymphocytes mildly depressed at $0.7 \times 10^9/L$) and C reactive protein at 326 mg/L.

This method used to measure troponin I comprised a two-site immunoenzymatic ('sandwich') assay process. The process is complex, but briefly, a clinical sample is added to monoclonal anti-cTnI antibody which is bound to paramagnetic particles. After incubation, a chemiluminescent substrate (Lumi-Phos 530) is added and the light generated by this reaction is directly proportional to the concentration of cTnI in the sample.

Renal and liver function tests were normal.

Subsequent tests found the patient to have a positive urinary *Legionella* antigen, for which co-amoxiclav and clarithromycin were continued. Sputum and blood cultures proved negative. Admission chest radiography appeared unremarkable, but a repeat chest X-ray only 4 h later showed widespread pulmonary opacification in the right middle and lower zones (figure 1). An echocardiogram revealed an ejection fraction of 51%, hypokinesia of the interventricular septum and trivial mitral regurgitation.

DIFFERENTIAL DIAGNOSIS

Myocardial infarction, myocarditis, pneumonia, generalised sepsis and *Legionella* infection (pneumonia).

TREATMENT

Clarithromycin was added to the original prescription of co-amoxiclav to cover for an atypical

Figure 1 Chest radiograph taken 4 h after admission showing widespread pulmonary opacification, predominantly in the right mid and basal zones.

To cite: Gill A, Dubrey SW. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-200489

pneumonia. Coamoxyclav was given for 5 days and clarithromycin continued for the full 10 days of the hospital admission.

OUTCOME AND FOLLOW-UP

The patient made a complete recovery on this combination of antibiotics and left the hospital 10 days following admission.

Recent outpatient coronary angiography showed established occlusion of the left anterior descending and circumflex vessels with numerous collaterals and a patent dominant right coronary artery. Additionally, the left internal mammary graft was occluded.

DISCUSSION

False positive troponin results are likely to occur when the true concentration lies close to the diagnostic threshold. However, the value of >95 000 ng/L reported in this case, overwhelmed the upper limit of normal, suggesting severe myocardial damage. This level of troponin was the highest value obtained since we commenced the use of this assay (Beckman-Coulter Access Accu TNI). Until now, only 12 results from 4437 samples have been recorded in excess of 40 000 ng/L (the three nearest values were 83 004, 63 437 and 62 448 ng/L). This biochemical result appeared incompatible with the clinical picture, even considering the results of the subsequent coronary angiogram. An echocardiogram revealed a mildly impaired left ventricle.

Spuriously raised troponin concentrations have been described in a number of circumstances, including pulmonary emboli, exacerbation of heart failure, myocarditis/pericarditis, sepsis and cardiac trauma.¹ *Legionella pneumophila* is a rare and under-recognised cause of an unusually high positive titre of cTnI. One study reported a raised troponin I level (Dimension Clinical Chemistry System (Dade Behring, RF421A)) in 46.7% of patients with legionellosis, who had negative creatine phosphokinase, creatine kinase-MB and cTnT levels. This report also described a significant association between cTnI levels and anti-*Legionella* antibodies, concluding that these antibodies can lead to interference in immunoassay techniques.³ The authors repeated their tests using a revised assay (Dade Behring, RxL cTNI reactive RF421C) that contained reagent modifications to minimise interference from heterophilic antibodies. The resulting repeat assay produced only two positive troponin I results out of the total 60 studied cases and these 2 values were only slightly higher than the cut-off (0.10 µg/L) at 0.12 and 0.14 µg/L. This reduced the troponin I positive rate from 46.7% to 3.3%, further indicating that *Legionella* heterophilic antibodies are responsible for these high troponin I results.

A recent case in the USA found a similar trend, whereby heterophile antibody interference in legionellosis led to an abnormally raised troponin I level.⁴

Legionella is an unusual bacterium, with significant interaction with man only since the introduction of water/environment management systems. Normally resident within amoebae, in man, *Legionella* generate in an intracellular vacuole that takes on an endoplasmic reticulum-type role. The resultant

production of many proteins are capable of mimicking many of the functional aspects of eukaryotic cells,⁵ and may explain how *Legionella* infections can produce heterophile antibodies. These antibodies bind with the reagent immunoglobulin producing an elevation of the troponin value. As the reagents used in troponin immunoassays are derived from immunoglobulins of other species, one method of checking if an elevated value is spurious is to request a repeat test using a different reagent assay.⁵

The diagnosis of acute myocardial infarction has become increasingly dependent on cardiac biomarkers and particularly cardiac troponins. *Legionella* is a not an uncommon respiratory tract infection, contributing to approximately 7% of pneumonias.⁶ *Legionella* infection, independent of sepsis or myocarditis, should now be considered as a cause of an elevated troponin result.

Learning points

- ▶ Troponins may be elevated for a number of reasons in the context of infection (severe sepsis and myocarditis being two of the reasons).
- ▶ In the case of *Legionella*, a third possibility needs to be considered due to interference with the actual assay from the production of heterophile antibodies.
- ▶ In itself, *Legionella* is an interesting organism, in that its interaction with man has really existed to any significant extent only for the past 50 years (since the use of water management and air conditioning systems).
- ▶ One method of checking if an elevated troponin value is spurious is to request a repeat test using a different reagent assay.

Contributors AG and SWD contributed to assembling the data, writing the case and discussion.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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