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CASE SERIES
Coronary intervention

Elevated cardiac troponin secondary to heterophile antibodies: a case series highlighting an underrecognized differential

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Background Heterophile antibody presence confounds troponin assay results, causing falsely elevated troponin levels. This rare phenomenon is an important differential to consider when evaluating patients with suspected acute coronary syndrome. We present a case series of three patients with similar clinical presentations where the presence of heterophile antibodies was confirmed.

Case summary We reviewed three patients from our hospital who presented with chest pain in a 12-month period. All patients were males aged 50–70. All patients had elevated troponin, and there was clinical concern for acute coronary syndrome in two patients. Two patients underwent coronary angiography during admission, and the third had a recent angiogram within the last 6 months. No obstructive lesions were found, and no alternative diagnoses were identified. Ultimately, the presence of heterophile antibodies was confirmed in all three patients.

Discussion Heterophile antibody presence is an important differential to consider in patients with unexplained troponin elevation. Once the presence of heterophile antibodies is confirmed, this aids in clinician decision-making and helps to guide investigations and treatment in future.

Keywords Heterophile antibody • Troponin • Chest pain • Acute coronary syndrome • Case series

ESC curriculum 3.1 Coronary artery disease • 3.2 Acute coronary syndrome

Learning points

- Heterophile antibodies and other molecules which interfere with troponin assays may cause false-positive troponin elevation and lead to unnecessary investigations and treatment.
- Clinicians should be suspicious of heterophile antibody presence in patients with persistently elevated troponin without a clear explanation.

Introduction

Cardiac troponin assays are crucial to the diagnostic evaluation of acute coronary syndromes (ACSs) worldwide, and abnormal troponin levels are part of the universal definition of acute myocardial infarction (AMI).[1] Troponin assays have evolved over the past 4 decades, aiming to maximize sensitivity for early detection of AMI.[2] The newest fifth-generation high-sensitivity cardiac troponin can identify troponin concentrations 1000 times lower than previous assays and have a negative predictive value for AMI nearing 100% upon repeat testing 3–6 h after presentation.[2,3] Despite improvements, these assays remain susceptible to false-positive results, and one of the most prevalent causes

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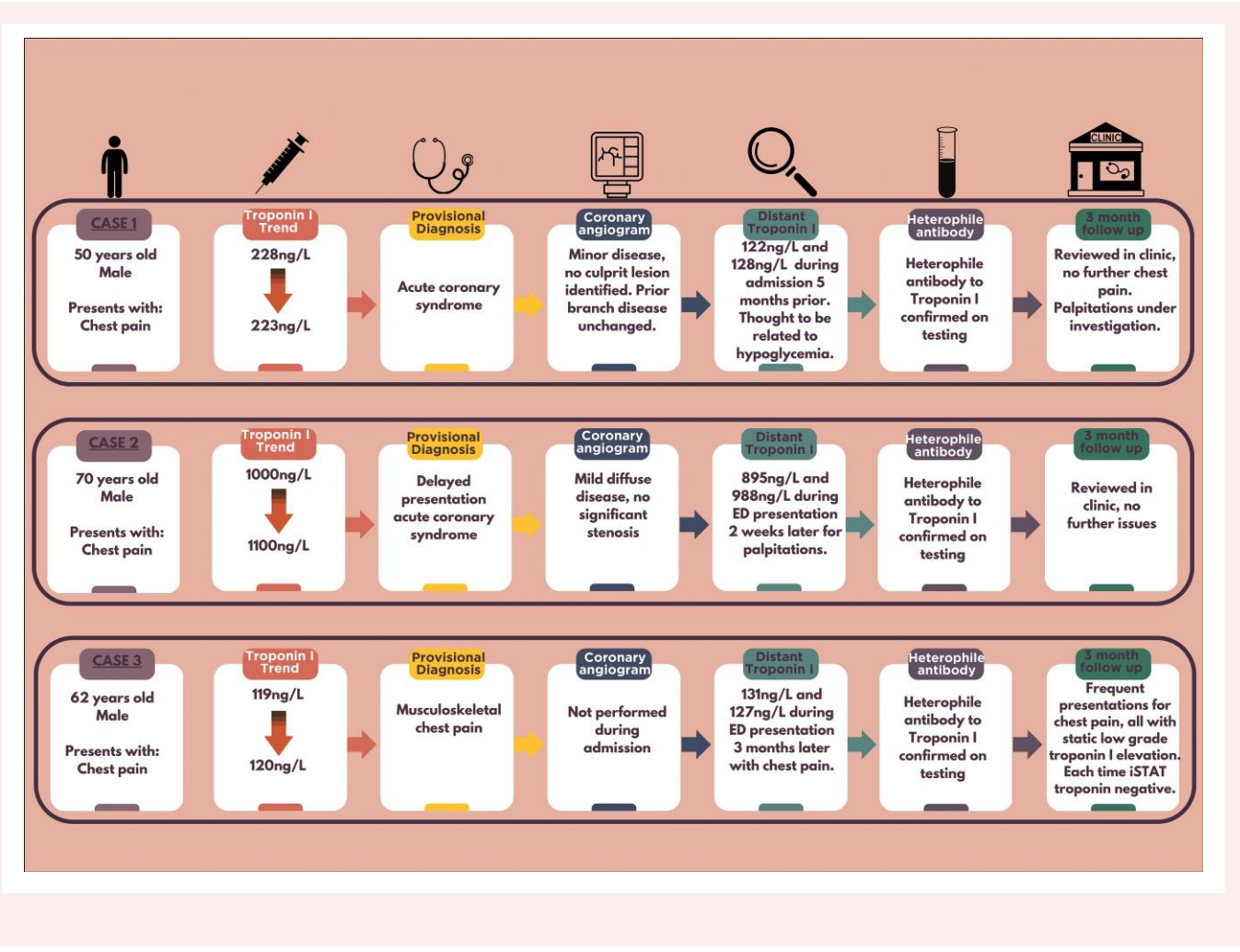
is heterophile antibodies.[1] Patients who produce heterophile antibodies present a unique diagnostic challenge when requiring evaluation for symptoms suggestive of ACS. This case series details three patients in whom the presence of heterophile antibodies to troponin assay was confirmed. Our cases highlight an underrecognized differential that carries significant clinical implications.

Summary figure



yo, years old; ACS, acute coronary syndrome; ED, emergency department. 1—normal range for troponin I in our institution is <50 ng/L.

Case presentation

Case 1

A 50-year-old man presented to the emergency department with chest pain and infrequent palpitations. The chest pain was described as left sided with radiation to the left arm and was self-limiting. The patient has a background of type 2 diabetes mellitus and 4 years prior underwent stenting with two drug eluding stents to the left anterior descending artery. Vital signs on admission were normal and clinical examination was unremarkable. Electrocardiogram (ECG) showed sinus rhythm without any ST-T changes (*Figure 1*). D-dimer was 1.1 mg/L, and serial troponin I results were 228 ng/L and 223 ng/L at the 3-h mark. Subsequent transthoracic echo was normal with an ejection fraction (EF) of 60%, no valvular abnormalities, and no regional wall motion abnormalities (RWMAs). Ventilation/perfusion scan revealed no evidence of pulmonary embolism. Coronary angiogram demonstrated patent stents with no significant in-stent restenosis and minor coronary disease elsewhere. No arrhythmia was detected on telemetry monitoring. Subsequently iSTAT troponin was found to be <0.02 μg/L and post immunosubtraction troponin I testing on initial blood samples found a true troponin I result of 11 ng/L (<50 normal range). The presence of heterophile antibodies was later confirmed by the laboratory post discharge. The patient was followed up in the cardiology clinic and had no further complaints of chest pain but still describes ongoing short-lived palpitations which are under further investigation.

Case 2

A 70-year-old man presented to the emergency department after being sent in by his general practitioner due to an abnormal troponin I result in the community. Two days prior to his admission, he had an episode of left-sided chest pain which was burning in nature and lasted approximately 20 minutes. There was no recent history of chest pain or any other illness. The patient previously underwent stenting of the posterior descending artery (PDA) in Thailand in 2013. Examination on arrival to the emergency department was unremarkable, and the

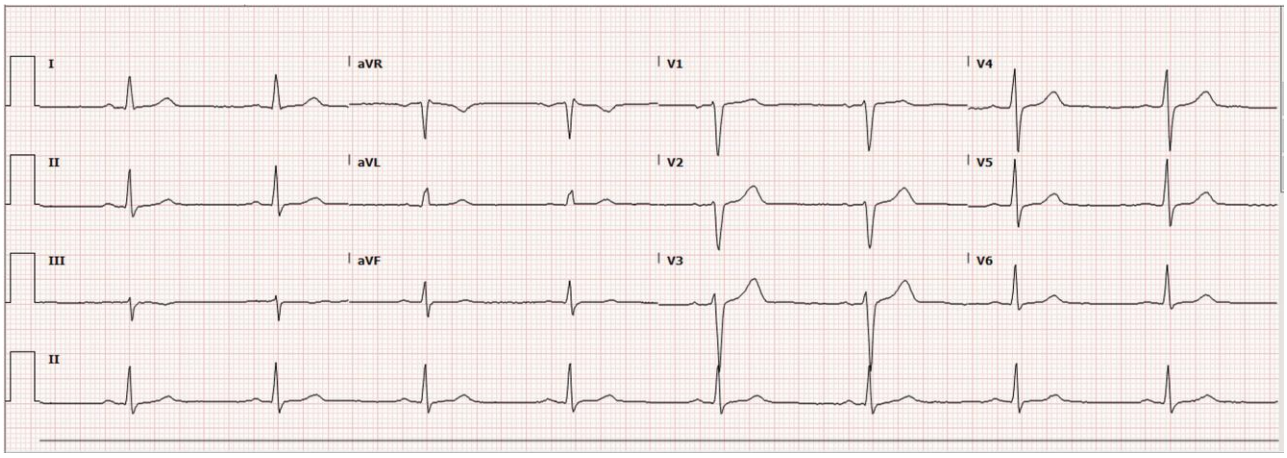


Figure 1 Presenting electrocardiogram for Case 1.

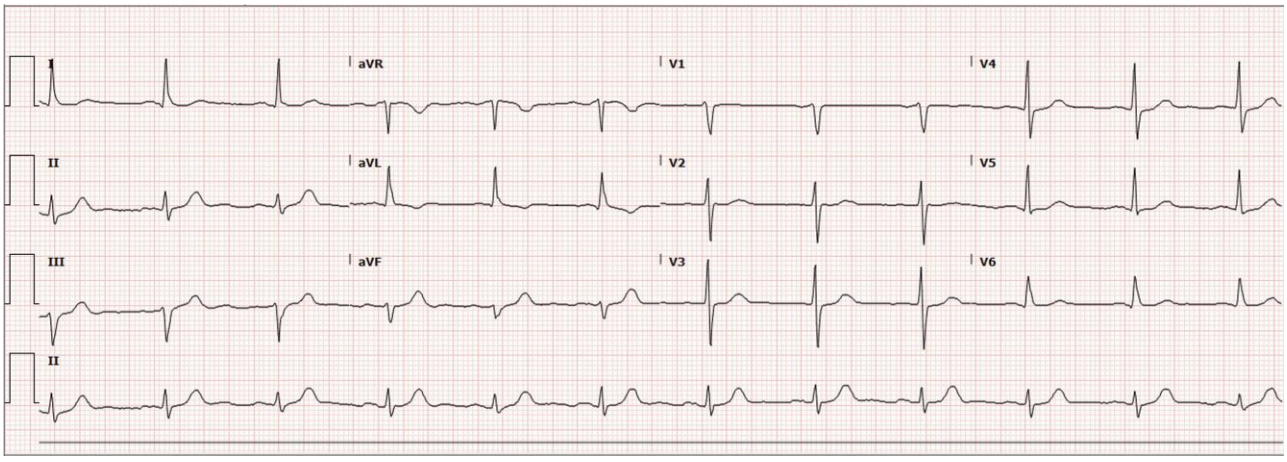


Figure 2 Presenting electrocardiogram for Case 2.

patient felt well with no recurrence of chest pain. Electrocardiogram showed normal sinus rhythm with isolated T waves inversion in aVL (*Figure 2*). Serial troponin I results were 1000 ng/L and 1100 ng/L taken 24 h apart. Transthoracic echo showed an EF of 55–60%, and there were no obvious RWMAs. The provisional diagnosis was felt to be a missed ACS. Coronary angiogram revealed no significant epicardial coronary disease, with at most 30% stenosis seen at the inlet of the previous PDA stent. After the angiogram, further investigation revealed a negative iSTAT troponin. Eventually, laboratory analysis confirmed the presence of heterophile antibodies and a post immunosubtraction troponin I result of 4 ng/L on initial bloodwork. In retrospect, the cause of the chest pain was most likely gastrointestinal in nature. Three months post discharge, the patient was seen in clinic and was well, with no further complaints.

Case 3

A 62-year-old male calls an ambulance and presents to the emergency department after 90 min of sudden onset, sharp left-sided chest pain whilst watching TV. On arrival, his pain had remitted to a dull ache after two sprays of GTN and was not fully relieved. This patient has a significant cardiac history with paroxysmal atrial fibrillation on apixaban, triple vessel coronary artery bypass grafting 14 years prior, and subsequent ischaemic cardiomyopathy, which after guideline-directed therapy and recent CRT-D implantation has stabilized his EF at 50–55%. This patient also has mild cognitive impairment. His ECG demonstrated a non-specific intraventricular conduction delay (*Figure 3*). On examination he was euvolemic, there were no murmurs, and vital signs were normal. Serial troponin I results were 119 ng/L and 120 ng/L taken 3 h apart. Given the significant burden of heart disease in this gentlemen, an echocardiogram was performed which demonstrated no RWMA. He was admitted overnight for monitoring on telemetry. This patient had frequent presentations to the emergency department with chest pain and elevated troponins. Recent coronary angiogram within the last 6 months demonstrated patent grafts. Based on this information, an iSTAT troponin was performed and found to be negative. Subsequent laboratory analysis revealed the presence of heterophile antibodies. This result has proven to be useful because the patient

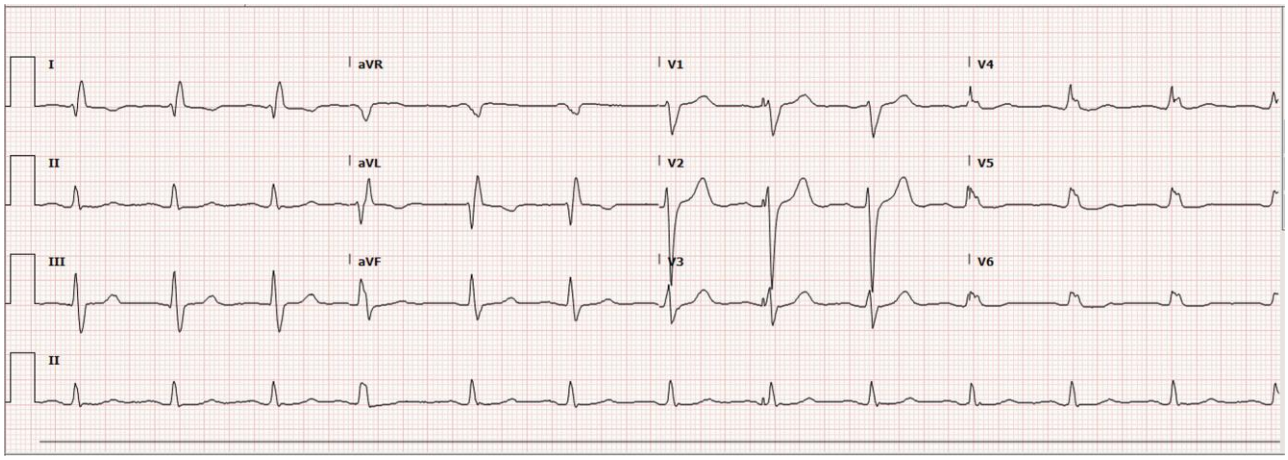


Figure 3 Presenting electrocardiogram for Case 3.

has since presented to hospital very frequently with atypical chest pain and low-grade static troponin elevation in keeping with the presence of heterophile antibodies.

Discussion

In this case series, we present three instances of elevated cardiac troponin secondary to heterophile antibodies, a rare scenario that adds difficulty to the workup of chest pain and suspected ACS. The phenomenon of antibody interference in immunoassays is well-documented and affects assays globally, irrespective of manufacturer.[4] Despite this, in clinical practice, heterophile antibodies are seldom considered as a differential for elevated troponin.[4,5]

The prevalence of heterophile antibodies remains uncertain, but studies estimate them to be present in 0.7%–3.7% of the population.[4,6] Individuals may develop these antibodies as a consequence of viral illness, exposure to animals (notably mice), vaccinations, autoimmune disorders (rheumatoid factor), and certain medications.[4,6] Heterophile antibodies are a class of endogenous antibodies characterized by their weak, non-specific activity against poorly defined antigenic targets and have a propensity to weakly bind multiple non-human animal immunoglobulins.[4,7] Unfortunately, most modern immunoassays also employ animal-derived immunoglobulins to bind cardiac troponin and generate a detectable signal for quantification.[5,6] Due to their multispecific binding potential, heterophile antibodies can inadvertently crosslink the assay's antibodies in the absence of troponin, giving rise to inconsistent and false-positive results.[4,6]

Since their discovery, assay manufacturers have implemented blocking antibodies to mitigate the likelihood of antibody interference.[2] However, this line of defence can still be overwhelmed by high serum concentrations of heterophile antibodies.[2] In fact, the prevalence of falsely elevated troponin I to diagnostically significant levels due to heterophile antibodies has been estimated to be 14.8%.[8] However, its concurrence with angina pectoris is rare.[8] Clinical suspicion is key for diagnosis to prevent unnecessary treatment or invasive diagnostic procedures. Clinicians should consider a false-positive result in patients where there is serial static elevation of troponin and no alternate cause. It is important to remember that many non-cardiac conditions such as intense exercise, renal disease, sepsis, stroke, subarachnoid haemorrhage, and severe anaemia can cause troponin elevation.[7] Often troponin elevation in these conditions occurs in the absence of electrical, echocardiographic, or angiographic evidence of myocardial ischaemia.[5] Our patients had no definite non-cardiac explanations for their troponin rise, and thus when repeat coronary angiography demonstrated clearly non-obstructive CAD, we proceeded to either test directly for heterophile antibodies or compare assays from a different manufacturer (iSTAT by Abbott) which are known to use different antibodies.

There still remains a distinct paucity of empirical data to inform when clinicians should suspect heterophile antibodies and proceed with specific testing. Notwithstanding this, our cases largely mirrored the clinical trajectory of previous case reports published on heterophile antibody-producing patients presenting with angina.[2,4,7,9,10] Patients in these reports predominantly underwent repeated angiographic evaluation or non-invasive imaging on the basis of symptoms and elevated troponin, especially if they had known ischaemic heart disease. Eventually, clinicians suspected heterophile antibodies and subsequently tested on a different assay.[2,4,7,9,10] The diagnostic probability of heterophile interference rises considerably when an alternative assay is negative for a raised troponin. When conflicting results are identified, laboratories should be contacted, so they may utilize heterophile antibody blocking agents or a method of serial dilution of the patient's serum to confirm the diagnosis.[7]

The current 2023 European Society of Cardiology guidelines on the management of ACS in patients presenting without persistent ST-segment elevation emphasizes the importance of integrating clinical presentation, ECG findings, and biomarker measurement.[11] Notably, the guidelines highlight that one-third of patients with non-ST-elevation ACS will have normal ECGs, necessitating clinicians to depend heavily on high-sensitivity troponin (hsTn) to make the diagnosis.[11] Our cases illustrate the complexity inherent in this pathway when heterophile antibodies confound the troponin assay. Following the aforementioned guidelines, our patient cohort repeatedly progressed into two distinct clinical trajectories: 'Observation' or 'Rule-in ACS'.[11] This necessitated, at minimum, hospital admission, with the latter group requiring further evaluation through non-invasive diagnostics or coronary angiography.[11] Whilst care is comprehensive under this pathway, without early recognition, these patients who produce heterophile antibodies are subject to frequent hospital stays and unnecessary invasive procedures and repeatedly undergo resource intensive workup for suspected ACS.[11]

No clear guidelines currently exist to streamline the evaluation of patients with known heterophile antibodies presenting with chest pain.

However, case reports have placed greater emphasis on the dynamic rise or fall of troponin to suspect ACS or utilizing an alternative assay such as in our cases where the patient had previously proven a normal troponin.[4,5]

Conclusion

Ultimately, this case series illustrates the diagnostic challenge posed by heterophile antibodies interfering in cardiac troponin assays which is an underrecognized cause of false-positive troponemia. Clinicians should have a high index of suspicion for interference when hsTns are persistently elevated but discordant with ancillary cardiac diagnostic modalities and the patient's clinical presentation. Early recognition and utilizing heterophile antibody screening in those with unexplained static troponin elevation could reduce the overall burden on susceptible patients and cardiac services alike, avoiding unnecessary hospital stays and overtreatment.

Lead author biography

James Millhouse is a final year cardiology advanced trainee in Queensland Australia. This year, he is finishing his training at the Princess Alexandra Hospital and hopes to pursue a career in interventional cardiology.

Consent: All patients have given their written informed consent for their information to be shared in this article in a de-identified manner for education purposes. This includes publication of data and images in compliance with the COPE guidelines.

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Data availability

This case series describes three clinical cases where all available data are presented in the manuscript. There is no original or third party data in this manuscript.

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