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About a « false-positive » case of elevated troponine levels: differential diagnosis

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Response to Reviewers:	The term "Troponine" has been corrected in the title: "Troponin". We have also verified the correct spelling throughout the text.

About a « false-positive » case of elevated troponin levels: differential diagnosis

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Case presentation

A 36-year-old woman presented to the Emergency department for chest pain and epigastralgia which had been evolving for 10 days. The pain was felt as an oppression, not related to any effort, not increased by deep breathing, nor when the patient was leaning forward. It was transient and did not irradiate. It was an inaugural episode. There were no other symptoms accompanying this pain. The patient had no particular medical or surgical history, nor any known addiction. In terms of her chronic treatment, we simply noted that an IUD was inserted in 2017. The clinical examination was normal, as were the admission parameters: apyrexia; normal blood pressure at 119/63 mmHg; heart rate at 72 beats per minute; and oxygen saturation at 99% in the ambient air. The biology showed an elevation of the high-sensivity cardiac troponin I (hs-cTnI) measured by immunoassay (Alinity, Abbott) at 1317 ng/L. The other cardiac markers were within normal limits. D-dimeres were normal at 194 µq/L, and there were no inflammatory syndrome. A check-up was carried out 3 hours later, and showed a persistent elevation of hs-cTnI to 1199 ng/L, without other biological disturbances. A first electrocardiogram was performed, showing a regular sinus rhythm at 60 beats per minute, normal atrioventricular conduction and non-significant inferolateral stiffening. The second tracing was similar. The thoracic angioscanner did not reveal any abnormality. The patient was then admitted to the Cardiology department for further investigations. A new biology was taken the day after admission and still showed an elevation of hs-cTnI to 1176 ng/L, with no other disturbance. Cardiac ultrasound showed normal function, with a left ventricular ejection fraction of 70%, homogeneous kinetics, no valvular defects, no stigma of pulmonary hypertension and a virtual pericardium. The heart rate holter did not reveal any arrhythmia. A coronary angioscan was performed to exclude the presence of a coronary dissection and was normal. In view of the onset of pyrosis, the work-up was also completed by a gastroscopy which revealed the presence of grade A oesophagitis and non-ulcerated antrite. Proton pump inhibitors

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Discussion

Troponins are structural proteins of the myocardial contractile system. They are almost exclusively located in myocardial muscle. There are 3 subunits: I, T and C. Only the first two forms are of interest in Cardiology because of their cardiac isoform.(4) Troponins are the most sensitive and specific biomarkers of myocardial damage. They are considered as the "gold standard" for the diagnosis of acute coronary syndrome and are also used for prognostic purposes in heart failure.(2)(4) Their elevation can be observed after 1 hour for hs-cTn and between 4 and 6 hours for conventional troponins, after the onset of myocardial cell necrosis, and the return to normal can take between 10-15 days.(1) However, similarly to all biological markers, it is essential that the result of the assay obtained in the laboratory correlates with the clinical context. Indeed, Troponin elevation at this level is a sign of myocardial damage but does not provide information about the underlying mechanism. The **Table 1** shows the various pathologies and situations that may be accompanied by an increase in troponins, whether due to a mechanism of "direct" or "indirect" myocardial damage.(1)(2)(5)(6)(7)(8)

Direct causes	Indirect causes	False positives
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Myocardial injury	Respiratory distress	Autoimmune disease
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Coronary artery vasospasm/dissection	Stroke	Vaccination
Cardioversion	Subarachnoid hemorrhage	Blood transfusion
Valvulopathy	Epilepsy	Dialysis
Tako Tsubo	Kidney failure	Laboratory mistake
	Chemotherapy	
	Rhabdomyolysis/intensive sport	
	Serious burn	
	Sepsis	

Table 1. False elevation of troponins from « directs » causes, « indirects » causes and « false positives »

In a small proportion of the population (~3.1%), heterophilic antibodies are present in the serum, which can interfere with the classical troponin assay.(2)(3) These IgM antibodies are directed against animal immunoglobulins included in the immunoassay. HAMA (Human Anti-Mouse Antibodies) are the most common cause of this type of interference. Their presence in serum may be transient or permanent. They may appear accidentally or be promoted by exposure to animal proteins. They are often found in people who are regularly in contact with animals, such as veterinarians, farmers or people who own pets. They may also occur in patients who have received therapy involving the administration of animal immunoglobulins, such as in the treatment of certain cancers by immunotherapy, after blood transfusion, CMV viruses, leukaemia,...(1)(5)(8)(4). Distorted elevation of troponin levels can also be observed in patients with rheumatoid arthritis. This phenomenon is very rare and accounts for about 1% of cases.(1)(9) Indeed, the presence of high levels of rheumatoid factor in the patient's serum can lead to interference with certain immunoassays and therefore to false-positive results.(9) It should be highlited that in approximately 5% of patients with high levels of hs-cTnI, circulating immunoglobulins form high-molecular-weight complexes with troponin I, which is then called macrotroponin. The same mechanism can also be observed with other proteins such as prolactin or TSH.(7) These complexes can mimic the epitopes of the target marker in the assay and distort the result (thereby leading to an overestimation of the biomarker level). This can be checked by treating the blood sample with polyethylene glycols which precipitate these complexes and thus correct the final result or with another immune complexe removal more specific against IgG, or IgG and IgM.(7)(10)(11)

In order to better understand the interference phenomena that can occur in troponin assays, it is useful to explain in more details the methods currently used in clinical chemistry lab for this purpose. Sometimes, interference can occur and lead to biased results because the antibodies used bind to other circulating molecules than those initially targeted such as

heterophilic antibodies, rheumatoid factor, macrotroponins I,... These interferences occur more frequently in hs-cTnI assays.(9) In order to avoid this type of inconvenience, various methods have been developed by laboratories. These include sample dilution, use of heterophilic antibody blocking reagents, polyethylene glycol precipitation, gel filtration in chromatography, and also protein electrophoresis and immunoelectrophoresis.(7) Troponin T testing (if available) may also be performed when there is doubt about an unexplained elevated troponin I level. When there is a clear discrepancy between the two results, a false positive may be suspected. However, it should be bore in mind that there are rare cases of elevated serum troponin T in the context of skeletal muscle disease with re-expression of this isoform. In this case, however, troponin I is not elevated, which still raises the suspicion of a false assay. Finally, to be complete, there may also be more common assay problems, such as a laboratory error, a haemolytic blood sample, or a faulty immunoassay kit. Of course, these cases are relatively rare because the integrity of the samples, the assay method and the equipment used are checked regularly and meticulously.

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The present case reminds us to keep in mind that patients presenting with an isolated elevation of troponin with a discordant clinical picture and reassuring complementary examinations, should suggest to the diagnosis of a false elevation of the marker. This should encourage the clinician to discuss the case with the clinical biology team and to carry out various tests in order to highlight the presence of potential interferences. With a diagnostic attitude aimed at harmonising the clinical and laboratory work, we will be able to reach a diagnosis of certainty more quickly in the future, thereby avoiding additional examinations, which can be invasive and costly, and sometimes have a negative impact on the patient's well-being.

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