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Case Report
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A Case of Persistent Troponin Release: Is it always a Marker of Myocardial Injury?

*Chiara Mainardi[1], Giulia Brunello[1], Mauro Boiago[1], Anna Baritussio[1], Renzo Marcolongo[2], Nicoletta Gallo[3], Monica Maria Mion[3], Mario Plebani[3] and Alida Linda Patrizia Caforio[1]**

[1]Department of Cardiac Thoracic Vascular Science and Public Health, Division of Cardiology, University-Hospital of Padova, Italy

[2]Department of Medicine, Hematology and Clinical Immunology, University-Hospital of Padova, Italy

[3]Department of Laboratory Medicine, University-Hospital of Padova, Italy

Abstract

Background: Syncope is a Transient Loss of Consciousness (TLOC) due to cerebral hypoperfusion, it shares many clinical features with many disorders and therefore it is encountered in many differential diagnoses. Our patient is a 33 years old man, former smoker, with a history of multiple episodes of TLOC and elevated high-sensitive Troponin I (hs-TnI) values.

Case Report: The patient reached medical assessment after the first episode of TLOC, in 2013, when he was diagnosed with clinically suspected myocarditis due to persistently elevated hs-TnI and elevated C-Reactive Protein (CRP), and based on Cardiac Magnetic Resonance (CMR) findings. The second episode was in 2017 when clinical and additional examinations concluded for syncope. The third episode was in August 2020. All these episodes were associated with persistently elevated plasma hs-TnI concentrations.

Conclusion: in this case neuromediated syncope was responsible for the recurrent TLOCs, while persistently elevated hs-TnI levels were associated with macro-troponin complexes formation, with no evidence of pathological implication.

Keywords: Macro-troponin complexes; Neuro-mediated syncope; Heterophile antibodies

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Correspondence:
Alida Linda Patrizia Caforio, Department of Cardiac Thoracic Vascular Science and Public Health, Division of Cardiology, University-Hospital of Padova, Italy, E-mail: alida.caforio@unipd.it

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Introduction

Transient Loss of Consciousness (TLOC) is defined as a state of real or apparent LOC with loss of awareness and responsiveness, often past amnesia, of short duration. Non-traumatic TLOC is classified into one of four groups: Syncope, epileptic seizures, psychogenic transient loss of consciousness, and a miscellaneous group of rare causes. Specific signs or symptoms can guide in the diagnosis of the etiology of TLOC, especially when syncope is suspected. Cardiac troponin is the most sensitive and specific available marker of ischemic and inflammatory cardiomyocyte injury, playing a central role in a wide spectrum of clinical conditions, although false positive results are described in the scientific literature. According to the Fourth universal definition of myocardial infarction, detection of an elevated Tn value above the 99th percentile URL is defined as myocardial injury.

Case Presentation

Our patient is a 33 years old man, former smoker, with a history of multiple episodes of TLOC at rest. The first episode took place in 2013, while he was having dinner and was preceded by general discomfort. It was of short duration with rapid return to consciousness and symptoms regression. Based on blood tests, showing elevated hs-TnI and elevated CRP, and on CMR, which showed focal mid-apical anterolateral epicardial and pericardial late gadolinium enhancement, he was diagnosed with clinically suspected myocarditis. Electrocardiogram (EKG) and echocardiogram did not show relevant pathological findings. The second episode was in 2017, with the same characteristics as the previous one and no other associated signs or symptoms. Blood sampling confirmed persistently elevated hs-TnI values, ranging with minimum and maximum between 73.6 ng/L to 103.0 ng/L (reference values 0.0 ng/L to 34.0 ng/L), negative inflammatory markers and weakly positive Anti-Intercalated Disk Autoantibodies (AIDA). CMR, echocardiogram, ambulatory EKG monitoring were normal. A neurological evaluation supported by electroencephalogram and brain magnetic

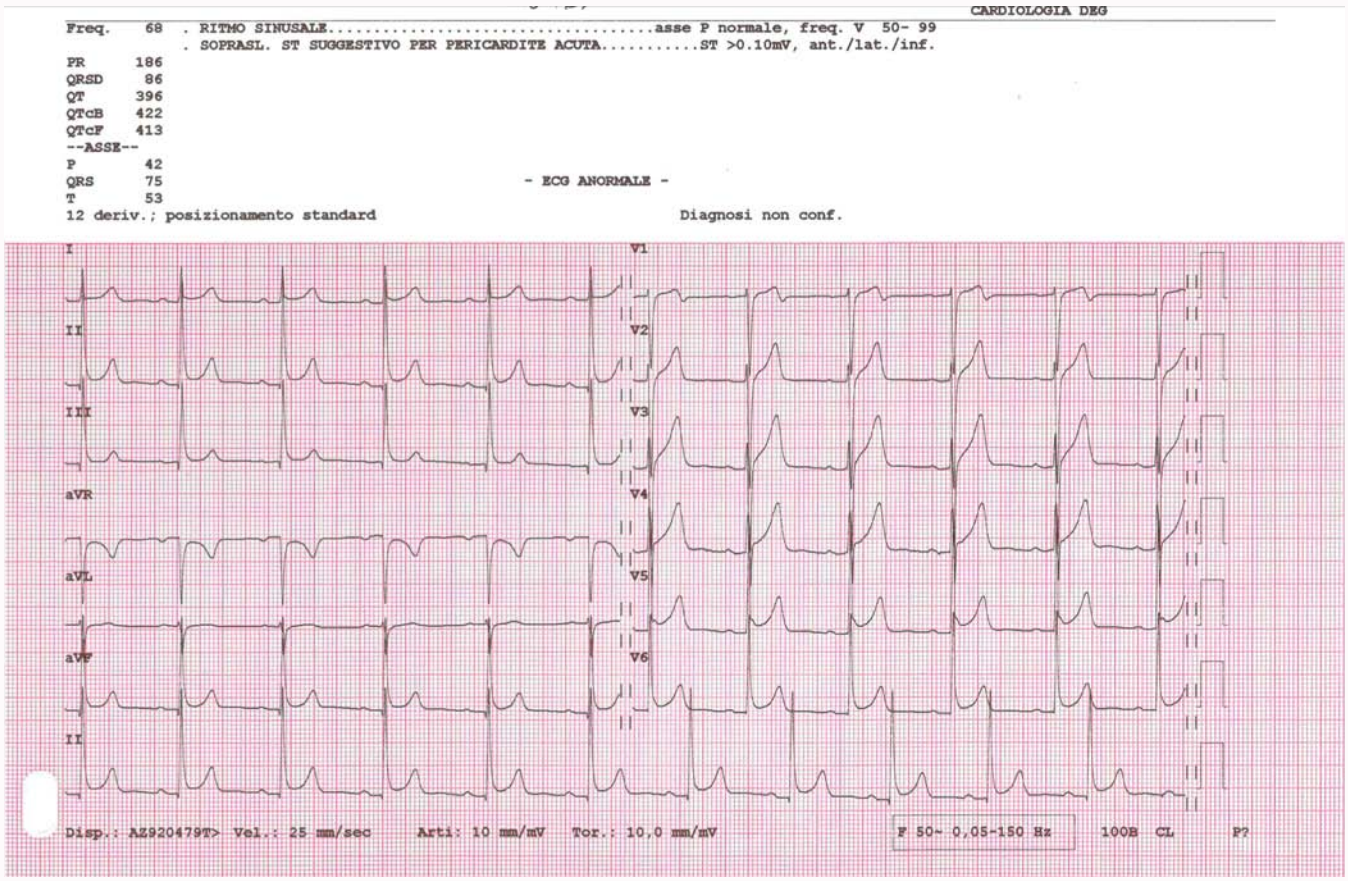

Figure 1: Cardiac MRI 2020, ECG 2020.

resonance imaging was inconclusive, corroborating the hypothesis of syncope. In August 2020 another episode of TLOC occurred, similar to the others. He was admitted to our ward, with no noteworthy signs or symptoms. First line tests, as EKG and echocardiogram, were unremarkable, but persistently elevated plasma TnI levels were found again (hs-TnI minimum and maximum 124.9 ng/L to 150.5 ng/L, reference values 0.0 ng/L to 34.0 ng/L). To exclude structural cardiac cause of TLOC, a new CMR was performed and resulted normal. A coronary computed tomography angiography was performed to rule out coronary artery disease, and only showed an intracoronary myocardial bridge of the left anterior descending artery. In-hospital continuous rhythm monitoring was inconclusive; no brady- or tachy-arrhythmias were detected. Regarding TLOC episodes, after a negative neurological evaluation, a tilt-test examination was performed which resulted positive for symptoms and fall in blood pressure, confirming the diagnosis of neuro-mediated syncope. Regarding the persistence of elevated plasma hs-TnI levels, other causes of myocardial injury were investigated: Neither professional exposure to cardio-toxic substances nor drug abuses were found. Moreover, heterophilic antibodies interference in hs-TnI assay was excluded using HBT ("Heterophilic Blocking Tube", Scantibodies Laboratory, Inc., Santee, CA, USA). Finally, further laboratory investigations revealed the presence of macro-troponin complexes leading to an increased half-life of circulating hs-TnI as well as its plasma concentrations (Figure 1).

Discussion

According to the 2013 European Society of Cardiology consensus, diagnostic criteria for clinically suspected myocarditis include clinical presentation (such as acute chest pain, dyspnea at rest or on exercise, unexplained arrhythmia, syncope or unexplained cardiogenic shock) and diagnostic criteria, including newly abnormal 12 lead EKG, myocardiocytolysis markers elevation, functional and structural abnormalities on cardiac imaging and presence of edema and/or late gadolinium enhancement of classical myocarditic pattern at tissue characterization by CMR [1]. TnI and TnT are the preferred biomarkers for the evaluation of myocardial injury and high-sensitivity (hs-TnI) assays are recommended for routine clinical use [2]. However, these biomarkers are not specific for the etiology of injury and a wide range of conditions are known to be associated with increased troponin values. These include: myocardial injury related to acute myocardial ischemia with atherosclerotic plaque disruption with thrombosis; myocardial injury related to acute myocardial ischemia due to oxygen supply/demand imbalance (caused by reduced myocardial perfusion, e.g. in coronary artery spasm, microvascular dysfunction, coronary embolism, coronary artery dissection, sustained bradyarrhythmia, hypotension or shock, respiratory failure, severe anemia, or caused by increased myocardial oxygen demand, e.g. in sustained tachyarrhythmia or severe hypertension with or without left ventricular hypertrophy); other causes of myocardial injury include cardiac conditions, e.g. heart failure, myocarditis, cardiomyopathy, Takotsubo syndrome, coronary revascularization procedure, cardiac procedure other than revascularization, catheter ablation, defibrillator shocks, cardiac contusion, and systemic conditions, e.g. sepsis, infectious disease, chronic kidney disease, stroke, subarachnoid hemorrhage, pulmonary embolism, pulmonary hypertension, infiltrative diseases, chemotherapeutic agents critically ill patients and strenuous exercise

[3]. Troponin kinetics in clinical context of suspected myocarditis can be similar to that observed in acute coronary syndromes (rise and fall) or can be flat, with remittent kinetics. Sometimes troponin can be persistently negative. Different kinetics and values of troponin could provide some hints about the etiology, but the clear identification of the cause usually requires a comprehensive approach including clinical, laboratory and instrumental findings. If instrumental findings don't corroborate the diagnosis of myocarditis, despite persistently elevated troponin values, further investigations are warranted [4]. In our case both in 2017 and in 2020 CMR, echocardiogram, ambulatory EKG monitoring were normal, therefore we looked for other explanations for symptoms and troponin elevation. With regards to troponin I elevation, false positive results are described, more often associated with fibrin clots and heterophilic Ab, Human Anti-Mouse Antibodies (HAMAs) or rheumatoid factor. Autoantibodies to cTnI or cTnT have been identified in roughly 10% of the healthy population and form complexes with troponin [5]. In this case, we demonstrated that macro-troponin complexes, formed by Ab, more of ten IgG, binding to troponin, mostly TnI, may be a cause of persistent elevation of troponin levels, due to its slow plasma clearance. One of the first cases of a false-positive TnI attributed to a macro-complex was reported in 2002, with authors suggesting the possibility that a modified molecule of cTnI induced the immunocomplex formation with a molecular mass similar to that of apolipoprotein B-100, leading to interference in TnI measurement. Therefore after the exclusion of the most common and harmful clinical causes, it may be advisable to consider the possibility of false positive troponin levels, especially when values are persistently and only mildly elevated and do not match with the clinical presentation [6]. To conclude, in this specific case, the association between nonspecific signs and symptoms, like TLOC and troponin elevation, resulted as independent elements in the final clinical diagnosis.

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