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PII: S0828-282X(21)00286-5
DOI: https://doi.org/10.1016/j.cjca.2021.05.010
Reference: CJCA 4053

To appear in: *Canadian Journal of Cardiology*

Received date: 28 February 2021
Accepted date: 21 May 2021

Please cite this article as: Tommaso D'Angelo MD , Antonino Cattafi MD , Maria Ludovica Carerj MD , Christian Booz MD , Giorgio Ascenti MD , Giuseppe Cicero MD , Alfredo Blandino MD , Silvio Mazziotti MD , Myocarditis after SARS-CoV-2 Vaccination: A Vaccine-induced Reaction?, *Canadian Journal of Cardiology* (2021), doi: https://doi.org/10.1016/j.cjca.2021.05.010

Myocarditis after SARS-CoV-2 Vaccination:

A Vaccine-induced Reaction?

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Short title: Myocarditis after SARS-CoV-2 Vaccine

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ABSTRACT

Vaccination plays an important role in the fight against the current pandemic of SARS-CoV-2, in order to minimize the spread of coronavirus disease 2019 (COVID-19) and its life-threatening complications. Myocarditis has been reported as a possible and rare adverse consequence of

different vaccines, and its clinical presentation can range from influenza-like symptoms to acute heart failure. We report a case of a 30-year-old male who presented progressive dyspnea and constrictive retrosternal pain after receiving SARS-CoV-2 vaccine. Cardiac magnetic resonance and laboratory data revealed typical findings of acute myopericarditis.

BRIEF SUMMARY

Myocarditis has been reported as a possible and rare adverse consequence of different vaccines, and its clinical presentation can range from influenza-like symptoms to acute heart failure. We report a case of a 30-year-old male who presented progressive dyspnea and constrictive retrosternal pain after receiving SARS-CoV-2 vaccine. Cardiac magnetic resonance and laboratory data revealed typical findings of acute myopericarditis.

Keywords: *autoimmunity; vaccine; MRI; myocarditis; COVID-19.*

CASE

A 30-year-old male presented at the emergency department complaining dyspnea, constrictive retrosternal pain, nausea and profuse sweating. Of note, the patient had suffered from fever (38.8°C) and arthralgia 72 hours earlier when he received his second dose of SARS-CoV-2 vaccine (mRNA BNT162b2), which was injected 21 days after the first dose.

The patient tested negative at nasopharyngeal swab testing for SARS-CoV-2, as required prior to hospital admission.

Anamnesis was negative for cardiovascular or metabolic disorders, and recent infectious diseases.

At physical examination he was afebrile, with moderate tachycardia (HR: 93 bpm) and normal

blood pressure (115/58 mmHg). At auscultation, neither lungs alterations nor heart murmurs were identified; oxygen saturation was of 99% on room air.

Laboratory data revealed elevated cardiac troponin-I (12'564.80 pg/mL; normal < 34.2 pg/mL), creatine kinase-MB (53.8 ng/mL; normal range: 0-5.2), lactate dehydrogenase (228 U/L; normal range: 125-220), activated partial thromboplastin time (75.2 seconds; normal range: 20-40), and C-reactive protein (39.6 mg/L; normal range: 0-5). White blood cells were 10.4 10^3/µl (normal range: 4.0-10.0), with mild eosinophilia 0.9 10^3/µl (normal range: 0.0-0.5). Serum levels of cardiac troponin-I, creatine kinase-MB and C-reactive protein during the first 72 hours from hospital admission are shown in **Figure 1**.

Electrocardiogram (ECG) showed subtle ST elevation suggestive of potential myocardial injury or pericarditis in V2-V4 with nonspecific T-wave changes in V5 and V6. Transthoracic echocardiography revealed preserved ejection fraction, mild pericardial effusion and segmental wall motion abnormality of the apical portion of interventricular septum. No coronary artery disease was found at coronary angiography. Cardiac MRI, performed 72 hours after hospital admission, revealed good systolic function and increased myocardial and pericardial signal intensity on T2-weighted STIR sequences (T2 ratio: 2.1; normal < 2). T1-weigheted PSIR sequences, performed 15 minutes after intravenous injection of gadolinium, showed subepicardial enhancement of the myocardium, suggesting a provisional diagnosis of myopericarditis (**Figure 2**).

Extensive infectious and rheumatologic workup was unremarkable. Virus serology did not show IgM antibodies nor fourfold increase of IgG antibodies for Epstein-Barr virus, Cytomegalovirus, Adenovirus, Enterovirus (Coxsackie A, Coxsackie B1) and human herpes 1 and 2 viruses.

A quantitative SARS-CoV-2 antibody assay was performed on an Abbott ARCHITECT platform (Abbott, Abbott Park, USA). The Abbott SARS-CoV-2 IgG II Quant-test (Abbott S IgG) quantified an

anti-spike post-vaccination titer > 40'000 AU/ml (range: 21 - 40'000 U/mL) at hospital admission, and equal to 8'392 U/mL at one month follow-up. On the other hand, the patient tested negative for SARS-CoV-2 infection (anti-nucleocapsid IgG antibodies) at both time points.

None of the patient's close contacts had tested positive to SARS-CoV-2 nasopharyngeal swab test or presented any COVID-19 related symptoms. Family history was also negative for rheumatological or genetic diseases.

The patient was initially treated with bisoprolol and acetylsalicylic acid, with progressive resolution of his symptoms. During his hospitalization, he also received prednisolone. Seven days after hospital admission a nasopharyngeal swab for SARS-CoV-2 was repeated, and the patient tested negative. Cardiac specific troponin I and creatine kinase-MB progressively decreased and he was discharged home with the recommendation to avoid intense physical activity.

DISCUSSION

The coronavirus disease 2019 (COVID-19) has spread rapidly into a pandemic. The global death toll has reached 3'154'603 (https://coronavirus.jhu.edu). Meanwhile, infections have passed 149.8 million worldwide and different reports have been suggesting that cardiovascular system is prominently affected by the infection.[1]

Vaccination is playing a crucial role to protect from COVID-19 and from its life-threating complications. However, vaccines can induce adverse reactions that in rare cases may lead to lethal consequences, such as myocarditis. These adverse events have been described more frequently in patients receiving smallpox vaccination, and very rarely in patients receiving vaccines for single-stranded RNA viruses such as influenza virus.[2,3]

Since MRI has become a mainstay in the diagnostic workup of patients with an infarction-like clinical presentation, it allows for a valid and non-invasive alternative to endomyocardial biopsy for diagnosis.[4] The presence of multiple areas of subepicardial late gadolinium enhancement, myocardial edema and pericardial thickening together with patient's ECG and laboratory data fulfilled the diagnostic criteria for myopericarditis.[4]

The pathophysiology of our case was more likely related to an autoimmune phenomenon. Although the exact trigger for autoimmune myocarditis is unknown, literature evidences suggest a "molecular mimicry" when the viral antigen resembles proteins on the myocardium. When autoreactive sensitization occurs, cytokines and lymphocytes migrate into the myocardial interstitial space inducing an inflammatory response.[3]

Another possible hypothesis is represented by a delayed hypersensitivity reaction, such as serum sickness–like reaction. In fact, the first vaccine dose may have presumably acquired sensitization. Moreover, the hypothesis of a delayed hypersensitivity after the second dose would be concordant either with the timing of symptoms, and with the mild peripheral eosinophilia seen in our case. A further hypothesis can be represented by eosinophilic myocarditis directly after immunization, which has been reported as an extremely rare event, despite the possible underdiagnosis due to its delayed development.[5]

Several cases of myocarditis associated with different vaccine administrations have been previously reported. In our case, we speculate that adverse reaction against the COVID-19 vaccine was responsible for the development of myocarditis due to its temporal relationship. However, substantial evidences other than temporal aspects still need to be provided to demonstrate the causality, such as histologically proven cases of autoimmune myocarditis following vaccination.

Finally, in light of the vast number of subjects receiving different doses of SARS-CoV-2 vaccine in

the next few months, clinicians should remain vigilant and suspect myocarditis in patients who present with cardiopulmonary symptoms after a recent vaccination.

FUNDING SOURCES

The authors have no funding sources to declare.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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FIGURE LEGENDS

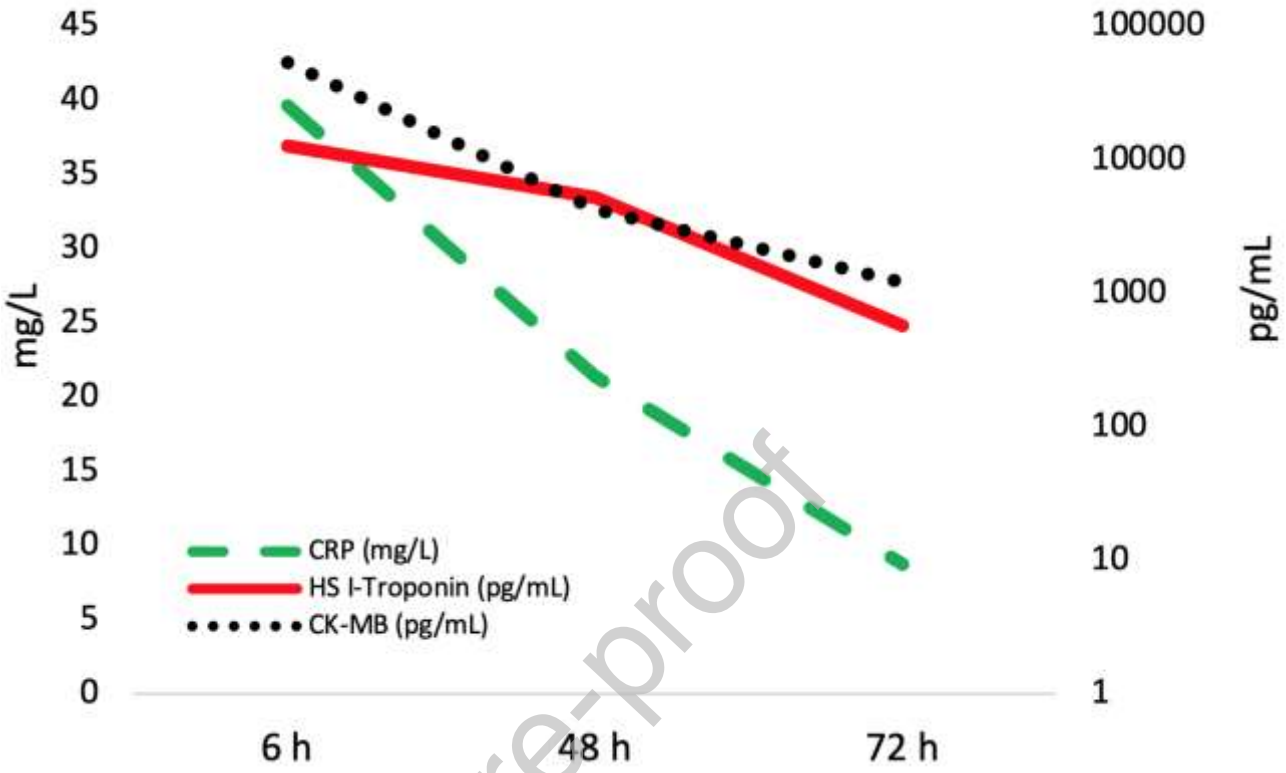
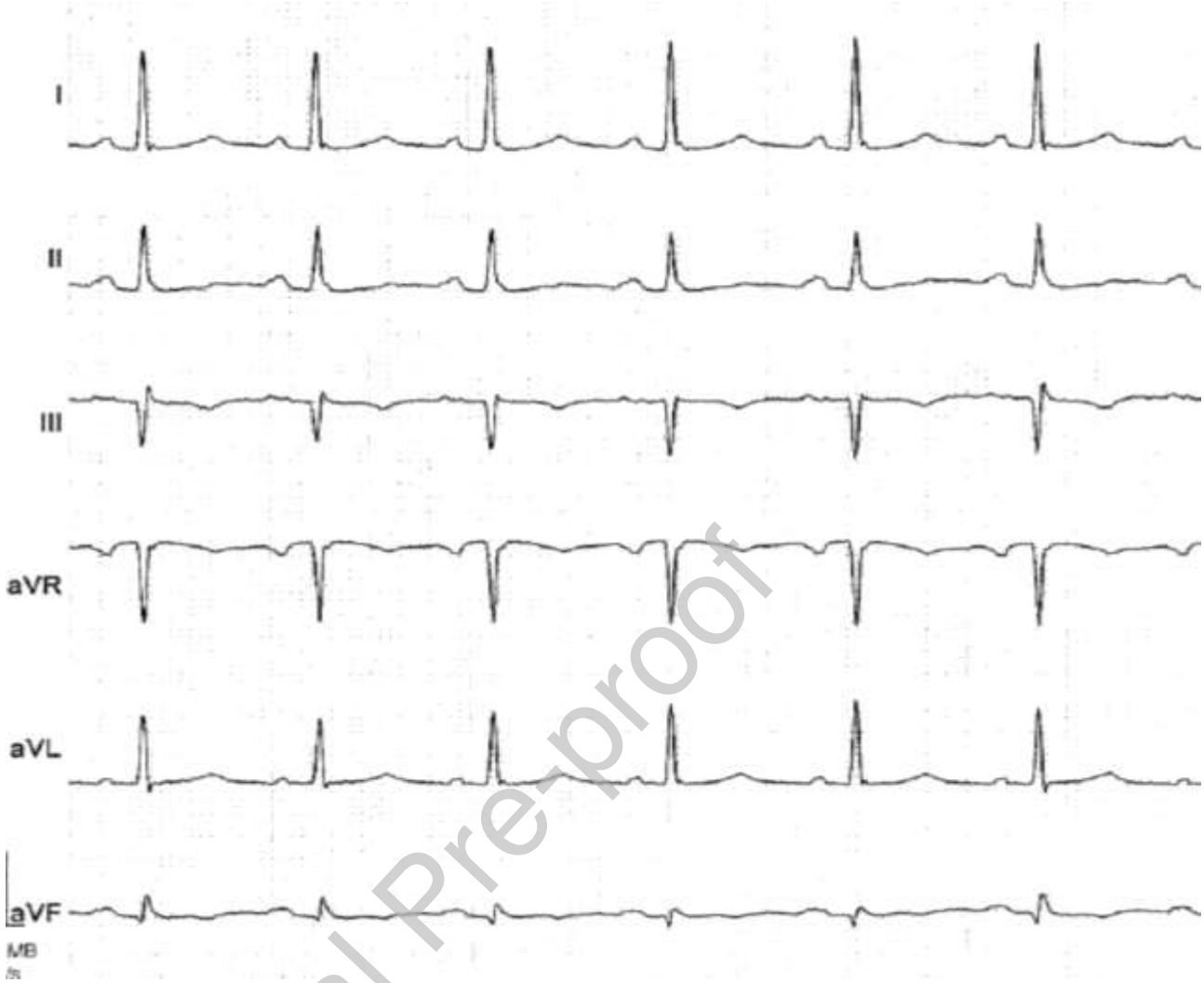
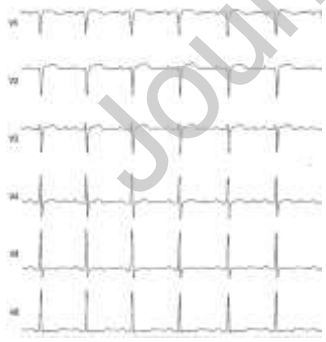
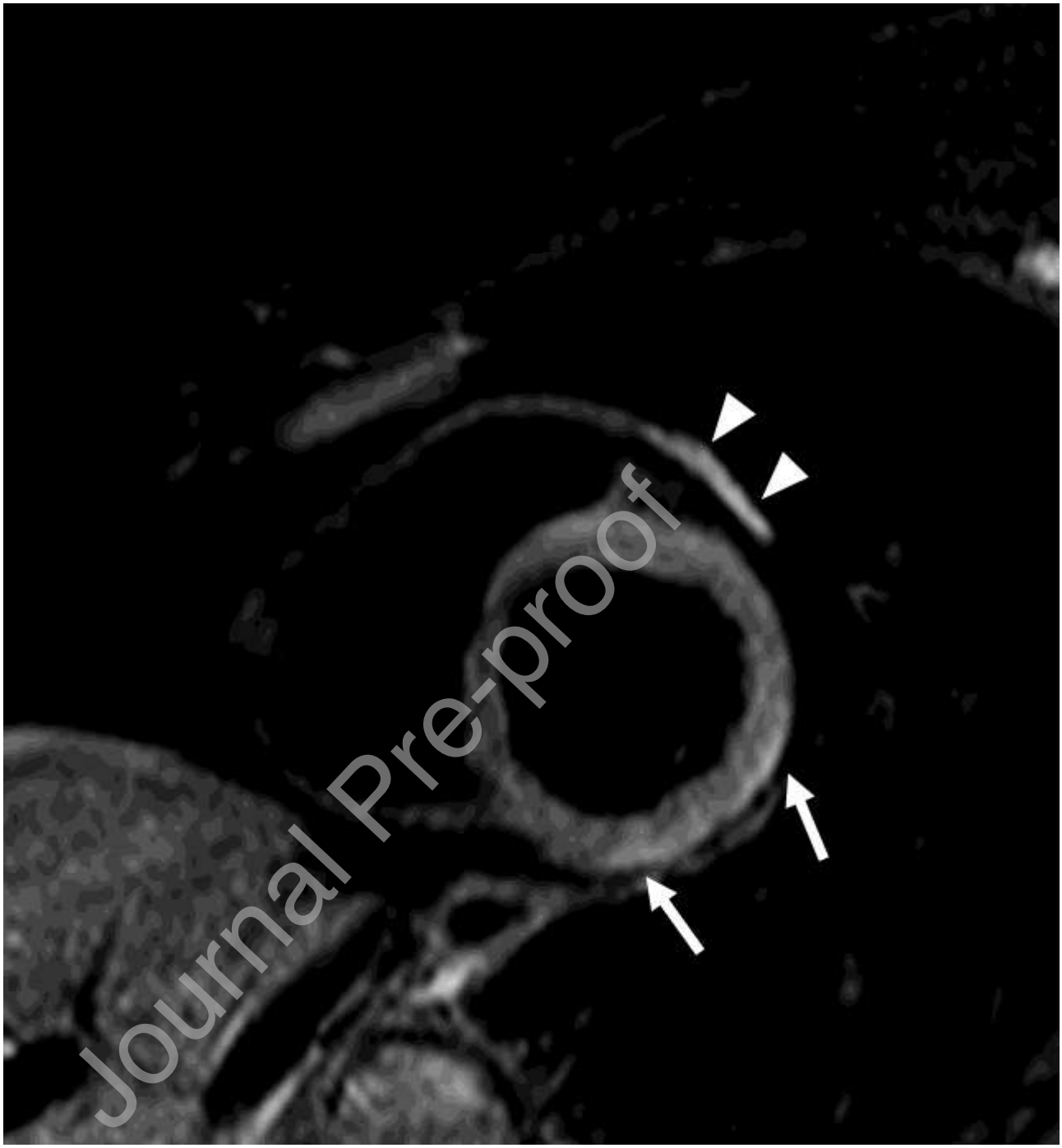


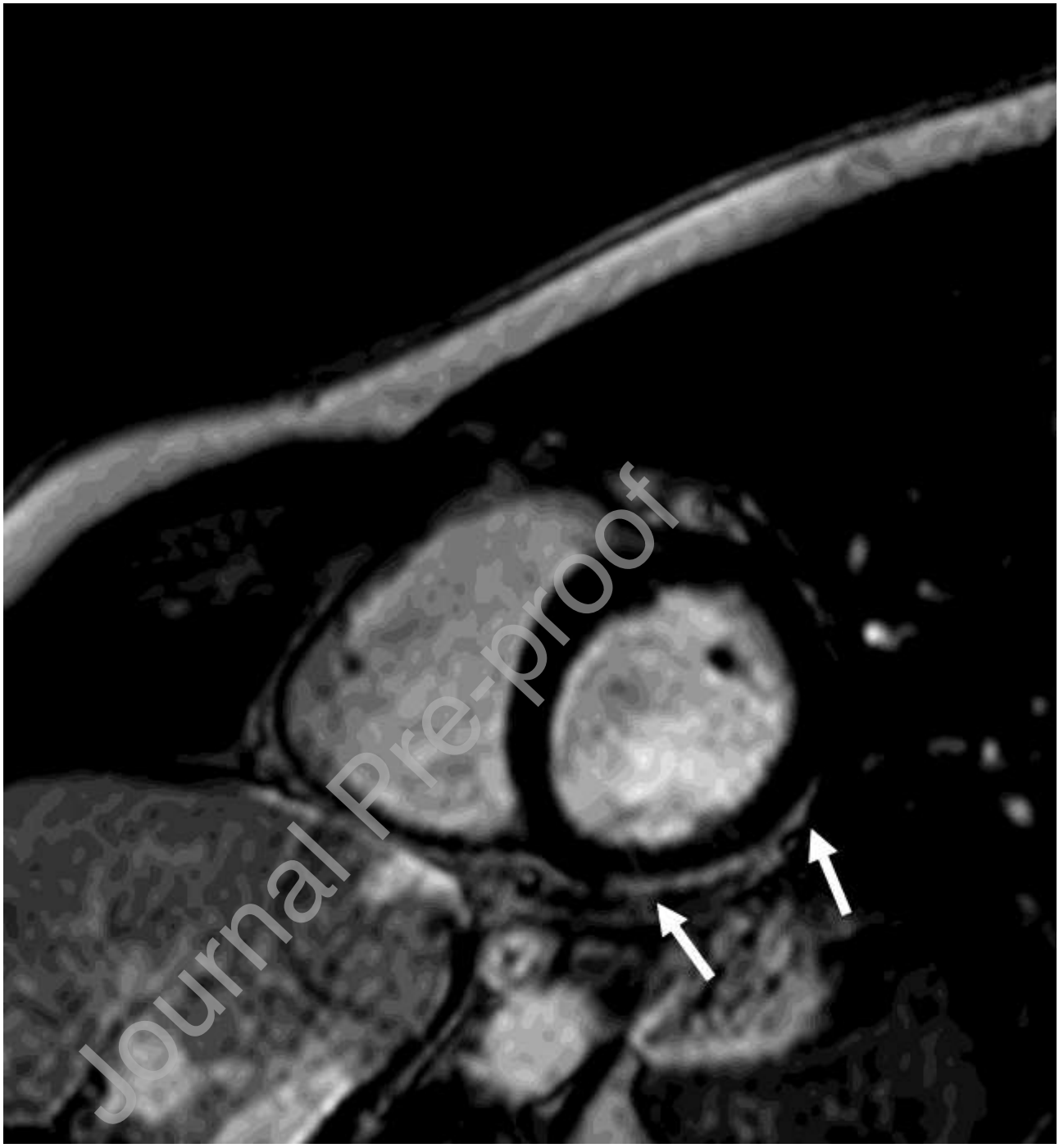
Figure 1

Graph showing the patient's serum levels of cardiac troponin-I, creatine kinase-MB and C-reactive protein during the first 72 hours from hospital admission.









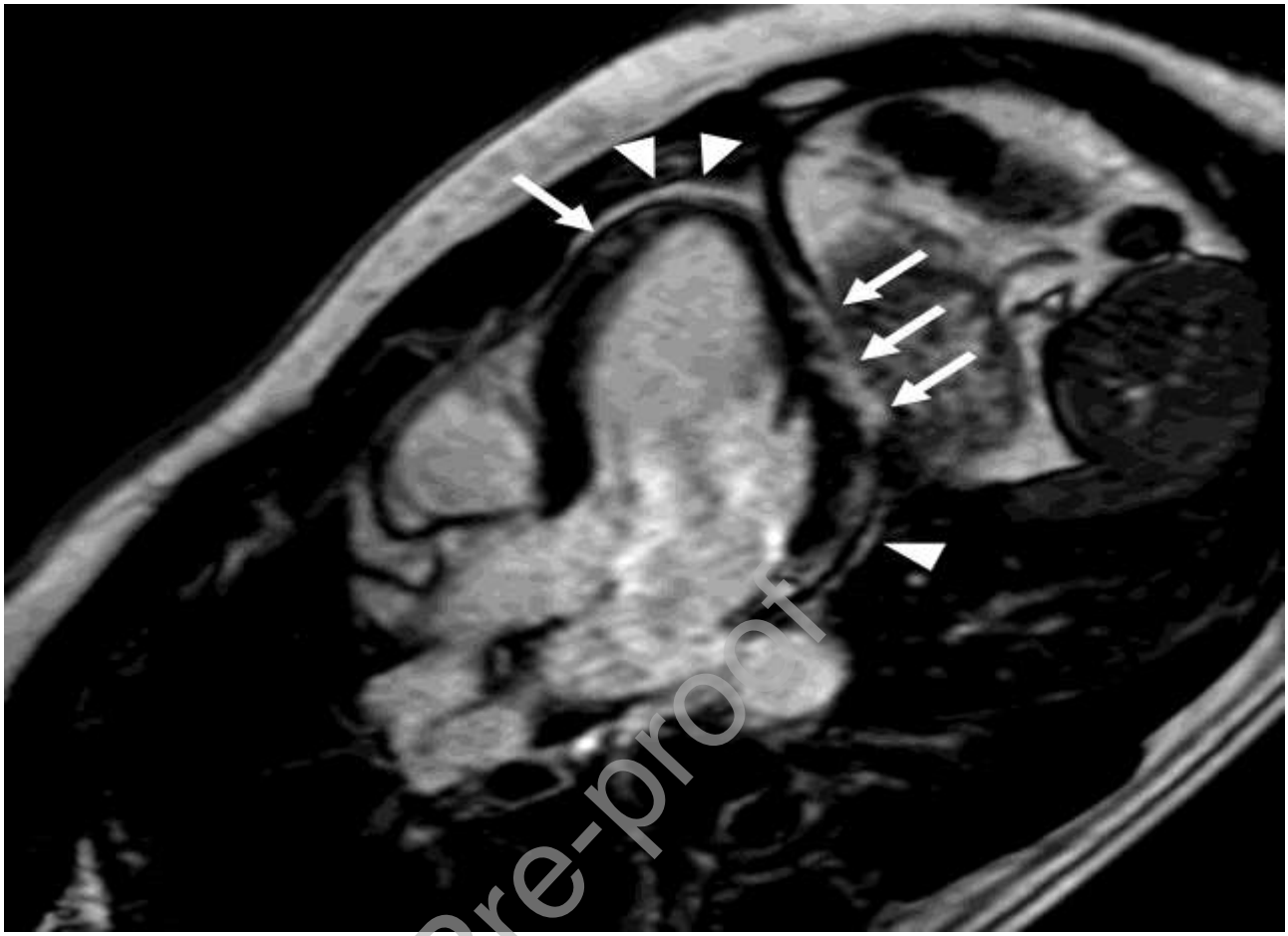


Figure 2

Twelve-lead electrocardiography on admission (**A, B**) showing subtle ST elevation suggestive of potential myocardial injury or pericarditis in V2-V4 with nonspecific T-wave changes in V5 and V6. Cardiac MRI T2-weighted STIR sequence (**C**) acquired along the basal short-axis view shows increased subepicardial signal intensity of the inferolateral myocardial segments (*arrows*). Increased thickness and signal intensity of pericardium is also shown (*arrowheads*).

T1-weigheted PSIR sequences performed along basal short-axis view (**D**), three-chamber view (**E**) and four-chamber view (**F**), show diffuse myocardial late gadolinium enhancement with subepicardial distribution (*arrows*) and sparing of the basal and mid septal segments; thickening and enhancement of pericardium can also be seen (*arrowheads*).