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A case of myopericarditis recurrence after third dose of BNT162b2 vaccine against SARS-CoV-2 in a young subject: link or causality?

Massimo Mapelli^{1,2*†}, Nicola Amelotti^{1,2†}, Daniele Andreini^{1,3},
Andrea Baggiano^{1,2}, Jeness Campodonico^{1,2}, Massimo Moltrasio¹,
Benedetta Majocchi¹, Valentina Mantegazza¹, Carlo Vignati¹, Valentina Ribatti¹,
Valentina Catto¹, Rita Sicuso¹, Marco Moltrasio¹, Gianluca Pontone¹, and
Piergiuseppe Agostoni^{1,2}

¹Heart Failure Unit, Centro Cardiologico Monzino, IRCCS, Via Parea 4, 20138 Milan, Italy

²Department of Clinical Sciences and Community Health, Cardiovascular Section, University of Milan, Via della Commenda 19, 20122 Milan, Italy

³Department of Biomedical and Clinical Sciences “Luigi Sacco”, University of Milan, Via G. B. Grassi 74, 20157 Milan, Italy

KEYWORDS

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The rate of post-vaccine myocarditis is being studied from the beginning of the massive vaccination campaign against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although a direct cause-effect relationship has been described, in most cases, the vaccine pathophysiological role is doubtful. Moreover, it is not quite as clear as having had a previous myocarditis could be a risk factor for a post-vaccine disease relapse. A 27-year-old man presented to the emergency department for palpitations and pericardial chest pain radiated to the upper left limb, on the 4th day after the third dose of BNT162b2 vaccine. He experienced a previous myocarditis 3 years before, with full recovery and no other comorbidities. Electrocardiogram showed normal atrioventricular conduction, incomplete right bundle branch block, and diffuse ST-segment elevation. A cardiac echo showed lateral wall hypokinesis with preserved ejection fraction. Troponin-T was elevated (160 ng/L), chest X-ray was normal, and the SARS-CoV-2 molecular buffer was negative. High-dose anti-inflammatory therapy with ibuprofen and colchicine was started; in the 3rd day high-sensitivity Troponin I reached a peak of 23000 ng/L. No heart failure or arrhythmias were observed. A cardiac magnetic resonance was performed showing normal biventricular systolic function and abnormal tissue characterization suggestive for acute non-ischaemic myocardial injury (increased native T1 and T2 values, increased signal intensity at T2-weighted images and late gadolinium enhancement, all findings with matched subepicardial distribution) at the level of mid to apical septal, anterior, and anterolateral walls. A left ventricular electroanatomic voltage mapping was negative (both unipolar and bipolar), while the endomyocardial biopsy showed a picture consistent with active myocarditis. The patient was discharged in good clinical condition, on bisoprolol 1.25 mg, ramipril 2.5 mg, ibuprofen 600 mg

*Corresponding author. Tel: +39 0258002930, Fax: +39 0258002266,
Email: massimo.mapelli@cardiologicomonzino.it

†The first two authors are shared co-first authorship.

three times a day, colchicine 0.5 mg twice a day. We presented the case of a young man with history of previous myocarditis, admitted with a non-complicated acute myopericarditis relapse occurred 4 days after SARS-CoV-2 vaccination (3rd dose). Despite the observed very low incidence of cardiac complications following BNT162b2 administration, and the lack of a clear proof of a direct cause-effect relationship, we think that in our patient this link can be more than likely. In the probable need for additional SARS-CoV-2 vaccine doses in the next future, studies addressing the risk-benefit balance of this subset of patient are warranted. We described a multidisciplinary management of a case of myocarditis recurrence after the third dose of SARS-CoV-2 BNT162b2 vaccine.

Introduction

The rate of post-vaccine myocarditis is being studied from the beginning of the massive vaccination campaign against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Myocarditis and pericarditis, mainly in male adolescents and young adults, have been reported more frequently than expected following receipt of the mRNA vaccines, BNT162b2 (Pfizer[®] vaccine) and mRNA-1273 (Moderna[®] vaccine).¹ Nevertheless, given the infrequency and the mild nature of the reported cases, the benefits of mRNA vaccination greatly exceed the small increased risk.¹ A review based on passive surveillance system showed that among over 192 million people who had received an mRNA vaccine between December 2020 and August 2021, there were 1626 cases that met the definition of myocarditis.² The majority of these cases occurred after the second dose, the median age was 21 years, and 82% occurred in males. Among the cases that have been reported, most were mild.³ Onset was generally within the first week after vaccine receipt, and most patients responded well to medical treatment and had rapid symptom improvement.⁴ Although a direct cause-effect relationship has been described,^{5,6} in most of the cases the vaccine pathophysiological role is doubtful. Moreover, it is not quite as clear as having had a previous myocarditis could be a risk factor for a post-vaccine disease relapse, and as individuals with a history of resolved myocarditis or pericarditis unrelated to Coronavirus disease 2019 (COVID-19) vaccination can safely receive an mRNA vaccine. The risk of this potentially serious adverse event and of many other serious adverse events is indeed substantially increased after SARS-CoV-2 infection.⁷ We present a case of myocarditis recurrence after the third dose of SARS-CoV-2 BNT162b2 vaccine in a patient with a previous acute myocarditis.

Case presentation

A 27-year-old man presented to the emergency department for palpitations and pericardial chest pain radiated to the upper left limb, on the 4th day after the third dose of BNT162b2 vaccine. He experienced a previous myocarditis 3 years before, preceded by symptoms of viral respiratory infection and treated with beta-blocker and angiotensin-converting enzyme inhibitor in the medium

term. Due to a complete clinical and echocardiography recovery, he discontinued the therapy in the past few months, and a follow-up cardiac magnetic resonance (CMR) performed 2 months before the current admission resulted normal. At presentation, electrocardiogram (ECG) showed normal atrioventricular conduction, incomplete right bundle branch block, and diffuse ST-segment elevation. A cardiac echocardiogram showed mild lateral wall hypokinesia with preserved ejection fraction (*Figure 1*). Troponin-T was elevated (160 ng/L), chest X-ray was normal, and the SARS-CoV-2 molecular buffer was negative. He was admitted to intensive coronary unit for monitoring where he remained asymptomatic, in the absence of ventricular arrhythmias or signs of haemodynamic instability. In the 3rd day high-sensitivity Troponin I reached a peak of 23000 ng/L. In relation to the ECG features (concave ST-elevation in multiple leads) and pain characteristics, a pericardial involvement was suspected, and high-dose anti-inflammatory therapy with ibuprofen and colchicine was started. A CMR was performed showing normal biventricular systolic function and abnormal tissue characterization suggestive for acute non-ischaemic myocardial injury (increased native T1 and T2 values, increased signal intensity at T2-weighted images and late gadolinium enhancement, all findings with matched subepicardial distribution) at the level of mid to apical septal, anterior, and anterolateral walls (*Figure 2*). In consideration of the myocarditis recurrence in a young patient, we decided to perform a left ventricular electroanatomic voltage mapping and endomyocardial biopsy (EBM). Mapping was negative (both unipolar and bipolar) (*Figure 3*), while the EBM (samples taken at the interventricular septum and left ventricular antero-lateral wall level) showed a picture consistent with active myocarditis: four fragments of left ventricular endomyocardium with cardiomyocytes of variable size between 14 and 19 microns, with perinuclear halos, interstitial oedema, and lymphomonocyte inflammatory cells also in clusters associated with myocyte necrosis, focal replacement fibrosis. The molecular screening, performed by polymerase chain reaction (PCR) and reverse transcriptase PCR in order to identify the potential presence of viral genome, was negative for adenovirus, cytomegalovirus, Epstein Barr virus, human herpes virus 6, herpes simplex virus, parvovirus, enterovirus/rhinovirus, cytomegalovirus, and influenza virus A and B. The patient was then discharged in good clinical conditions, on bisoprolol 1.25 mg o.d., ramipril 2.5 mg

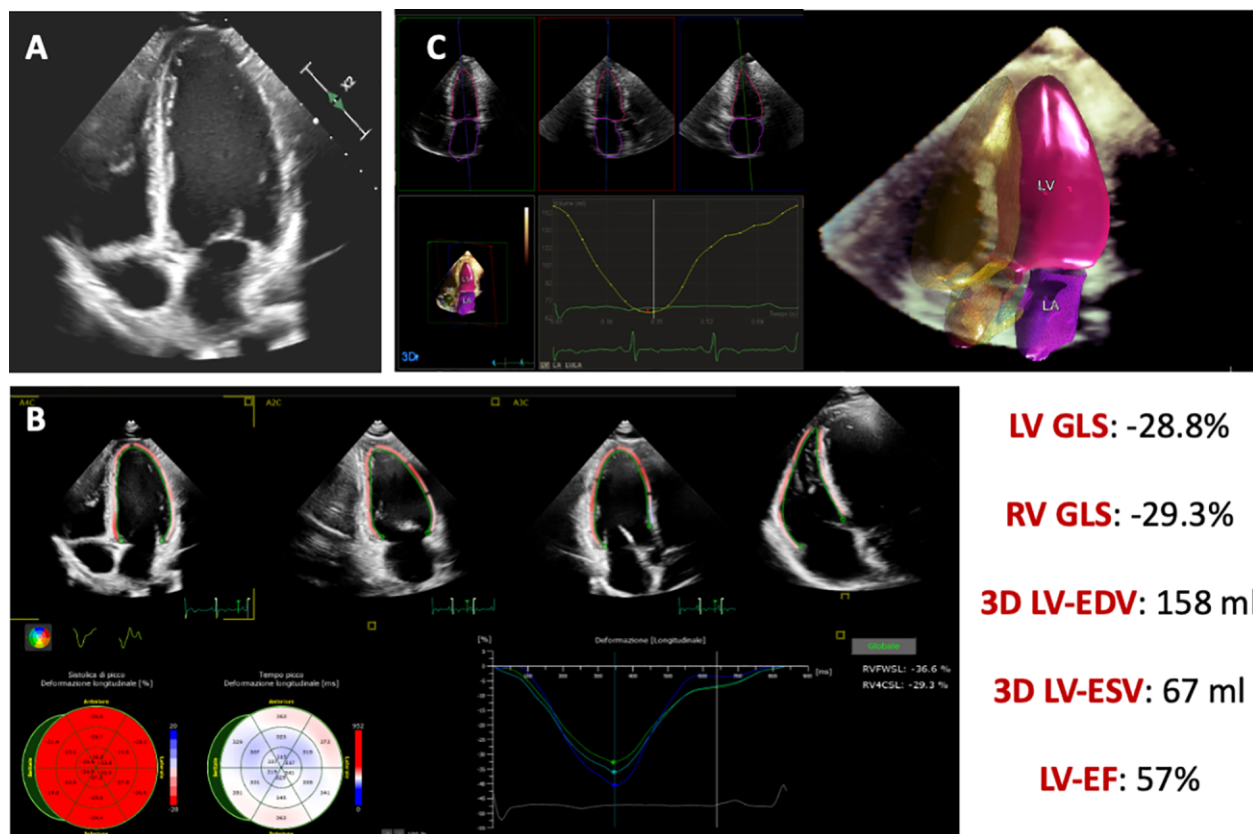


Figure 1 Echocardiographic findings. Transthoracic echocardiography showed normal two-dimensional biventricular dimensions, function (A), and global longitudinal strain values (B). Three-dimensional echocardiography confirmed the absence of left ventricular dilatation or dysfunction. EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; GLS, global longitudinal strain; LV, left ventricle; RV, right ventricle.

b.i.d., ibuprofen 600 mg three times a day, colchicine 0.5 mg b.i.d., lansoprazol 30 mg (for 1 month), and enoxaparin 6000 UI s.c twice a day (for 1 month, as a thrombotic prophylaxis after left ventricular biopsy). Proper indications on anti-inflammatory therapy weaning were given, as well as indications concerning avoidance of strong physical activity for 6 months. He was evaluated in the outpatient clinic 1 month after discharge: the ECG showed sinus rhythm, heart rate 62 b.p.m., normal PR interval (150 ms), stable incomplete right bundle branch block, QTC of 370 ms, and normal ventricular repolarization. Blood tests showed Troponin I 45.60 ng/L and Brain Natriuretic Peptide (BNP) 35 pg/mL. A full immunology screening was negative. He underwent a positron emission tomography-computed tomography which excluded active inflammation and therefore, after the case was discussed in heart failure team, steroid therapy was not started. There was also agreement that an eventual further SARS-CoV-2 vaccination (4th dose) will be discussed in future based on upcoming studies.

Discussion

We presented the case of a young man with history of previous myocarditis, admitted with a non-complicated acute myopericarditis relapse occurred 4 days after SARS-CoV-2 vaccination (3rd dose). In literature, most vaccine

myocarditis has been described after the second dose, and data on the incidence of myocarditis after the third dose are scarce.⁸ Cases of myocarditis recurrence temporally associated with the vaccine have also been described.⁹ Despite the observed low incidence of cardiac complications following BNT162b2 administration,¹⁰ and the lack of a clear proof of a direct cause-effect relationship,⁶ we think that in our patient this link can be more than likely. No other triggers were found, and the onset of symptoms related to the administration of the vaccine was compatible with timing reported in the literature.⁴ Data collected retrospectively in adolescent and young adults¹¹ showed that almost all the patients presented with chest pain, with symptom onset a median of 2 days after vaccine receipt, which the ECG was abnormal in 70% of the cases (ST-segment elevations or T-wave abnormalities), which CMR imaging was abnormal in 77% (late gadolinium enhancement and myocardial oedema), and that systolic function on echocardiogram was often within the normal range (80% of the subjects). These data are perfectly compatible with our case. Even if we were not facing with myocarditis complicated by heart failure, malignant arrhythmias, or conduction blocks, due to recurrence of myocarditis after 3 years, we decided to perform an electrophysiological study with electroanatomic voltage mapping and EBM to obtain histological data to guide therapy. Large, randomized trials on acute myocarditis treatment (i.e. exploring

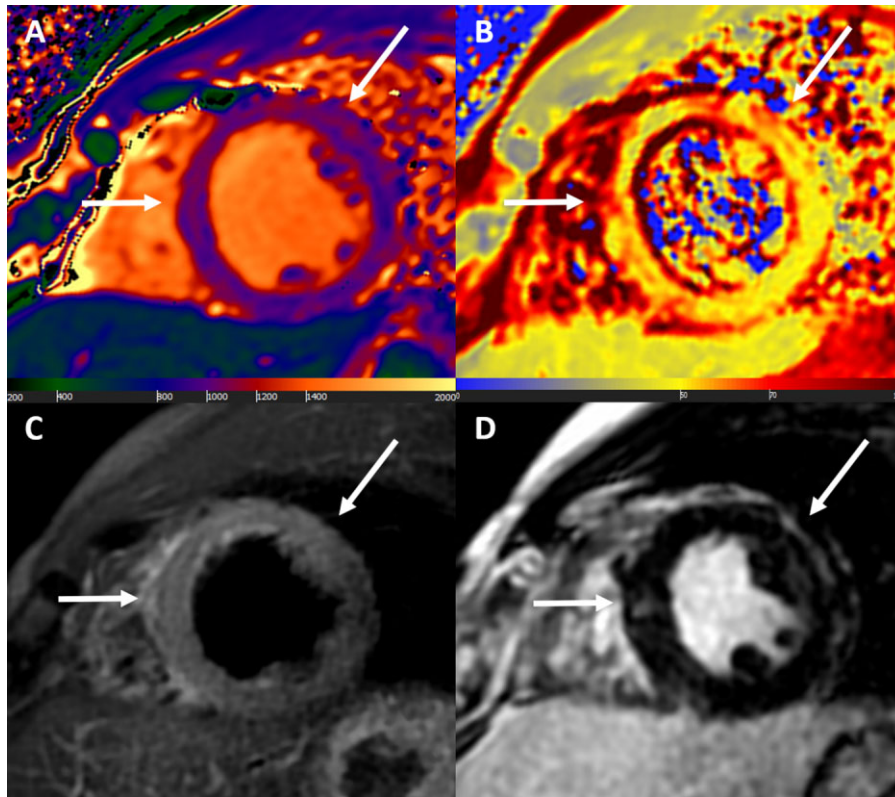


Figure 2 Cardiac magnetic resonance findings. Acute non-ischaemic myocardial injury at mid to apical septal, anterior, and anterolateral walls. (A) Increased native T1 values (up to 1260 ms); (B) increased T2 values (up to 71 ms); (C) increased signal intensity at T2-weighted images; and (D) non-ischaemic late gadolinium enhancement. All abnormal findings have matched subepicardial distribution (white arrows).

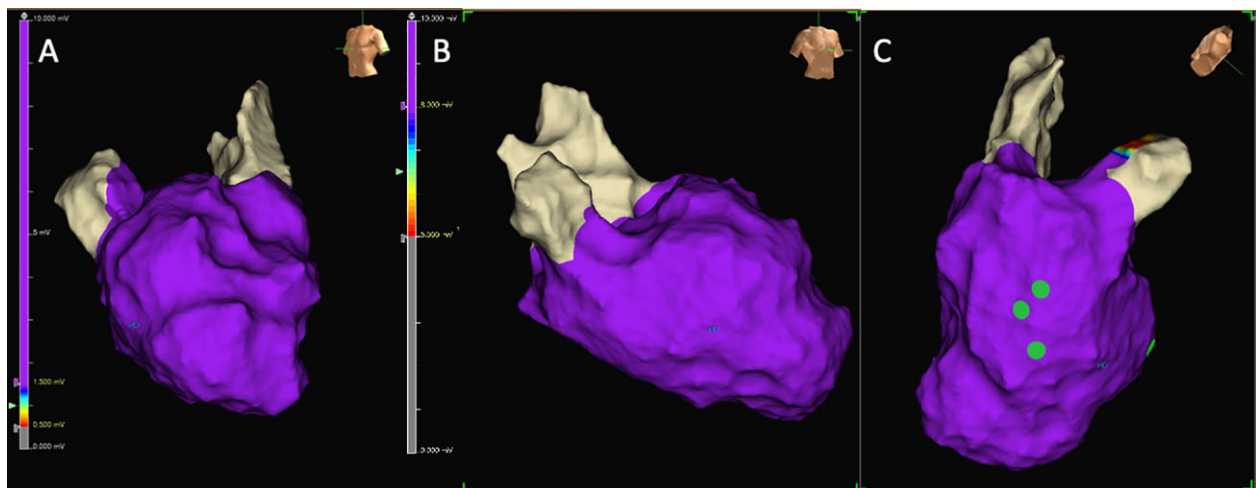


Figure 3 Electroanatomic voltage mapping of the left ventricle. Bipolar (A; in purple—left anterior oblique view) and unipolar (B; in purple—right anterior oblique view) electroanatomic left ventricular voltage mapping was completely normal. The green circles (C) represents the sites of bioptic samples.

the prognostic role of corticosteroids or other immunosuppressants) are missing. In this case, based on the initial clinical suspicion of acute pericarditis, the patient was already started on non-steroidal anti-inflammatory therapy, and we decided not to make further changes to the treatment also due to the uneventful clinical course. At 2-month follow-up, the patient is fine, with no signs or symptoms of heart failure, arrhythmias, and recurrent myocarditis.

Notably, 5 weeks after the discharge, he tested positive for SARS-CoV-2 infection at a nasopharyngeal swab performed just for screening purpose. The disease had a completely asymptomatic course even from a respiratory and cardiovascular point of view, indirectly confirming the excellent efficacy of the vaccination in preventing serious illness. In our case, the patient's clinical evolution was favourable and a full multidisciplinary evaluation has been done. It

would be very difficult to decide what to advise in the possible need for additional SARS-CoV-2 vaccine doses in the next future. For those who develop myocarditis or pericarditis following a first dose of an mRNA vaccine, it is suggested to postpone the second dose until the episode has completely resolved if the risk of severe COVID-19 is high.¹² Although our patient cannot be strictly classified as being at high risk for severe SARS-CoV-2 induced disease, he experienced a myocarditis relapse, and it is well known how cardiac complications following SARS-CoV-2 infection, including myocarditis, can be equally serious.¹³ In this case, the risk-benefit ratio is very balanced, and it is really difficult to determine which side it hangs the most.

Although cases of acute myocarditis associated to mRNA vaccines are already reported, to the best of our knowledge, a case of myocarditis recurrence after the third dose of BNT162b2 has not been described previously. Moreover, our case is emblematic of how extraordinary situations such as a pandemic (and the consequent mass vaccination campaign) can lead clinicians to have to make complex decisions on issues that have not been fully clarified yet, emphasizing the need for a real personalized patient management in the absence of validated guidelines or clear consensus.

Conclusion

We described a multidisciplinary management of a case of myocarditis recurrence after the third dose of SARS-CoV-2 BNT162b2 vaccine in a young male patient. Although not detracting in any way from the balance in favour of vaccination, this case opens questions about the risks of recurrence of post-vaccine myocarditis in patients with a previous cardiac inflammatory episode, a population in which the risk-benefit evaluation may be complex.

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Data availability

All data are incorporated into the article.

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