

CASE SERIES

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Two Cases of Acute Myocarditis in Young Male Adults After mRNA Vaccines Against COVID-19: Similarities and Differences

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ABSTRACT

Background: The advent of the new coronavirus SARS-CoV-2 has created unprecedented situations, both in terms of health and socio-economic level, worldwide. The emergence of vaccines against this highly contagious virus has raised hopes for its effective inhibition. The efficacy of vaccines, in more than a year of their application in clinical practice, is indisputable, both in terms of reducing serious hospitalizations and deaths, especially in high-risk populations. As with any new medication, the quest and investigation for side effects are reasonable. Myocarditis is one of the extremely rare side effects reported in mRNA vaccines, especially in young males. **Case presentation:** We present two cases of myocarditis that occurred in our hospital in a short time between them and compare them point by point to identify similarities and differences in order to draw conclusions about the severity of this side effect and its outcome. **Conclusion:** The benefits of vaccination against Covid-19 outweigh possible untoward effects and especially myocarditis. Health workers must close monitor the vaccinated patients for possible future cardiovascular complications.

Keywords: Myocarditis, vaccine, SARS-CoV-2, COVID-19, side effects.

1. BACKGROUND

Vaccination seems to be the most effective strategy the COVID-19 disease to be confronted. The mRNA-1273 (Moderna, Cambridge) vaccine and the BNT162b2 (Pfizer, New York) are the two mRNA vaccines approved for the global pandemic of coronavirus disease 2019 (COVID-19). Besides most common symptoms, such as fever, cough, fatigue, and transient loss of smell or taste, infection with the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) provokes severe symptomatology, such as breathing difficulties or shortness of breath, neurological manifestations or confusion, and chest pain (1). The latter is mainly due to myocarditis or pericarditis. Myocarditis has been implicated with an immune mechanism in both mRNA vaccines, especially in young males. Although the risk of myocarditis is up to six times less after vaccination compared with COVID-19 infection, acute chest pain that may occur a few days after vaccination should be investigated for myocarditis (2).

2. OBJECTIVE

We present two cases of myocarditis in two young male adults that visited our hospital in less than one-month time: the first one four days after the second dose of the mRNA-1273 vaccine and the second one seven days after the booster dose of the BNT162b2 vaccine following prior COVID-19 infection.

3. CASE PRESENTATIONS

Case 1 presentation

A 28-year-old man presented to our hospital with severe constant chest pain started six hours before, with no fluctuations. He was a healthy, non-smoking adult with no history of cardiovascular disease or obesity (BMI 23.8 kg/m²). There was no known family history of cardiovascular or autoimmune disease. The patient had received the second dose of the mRNA-1273 vaccine four days before. The electrocardiogram (ECG) showed marginal ST-segment el-

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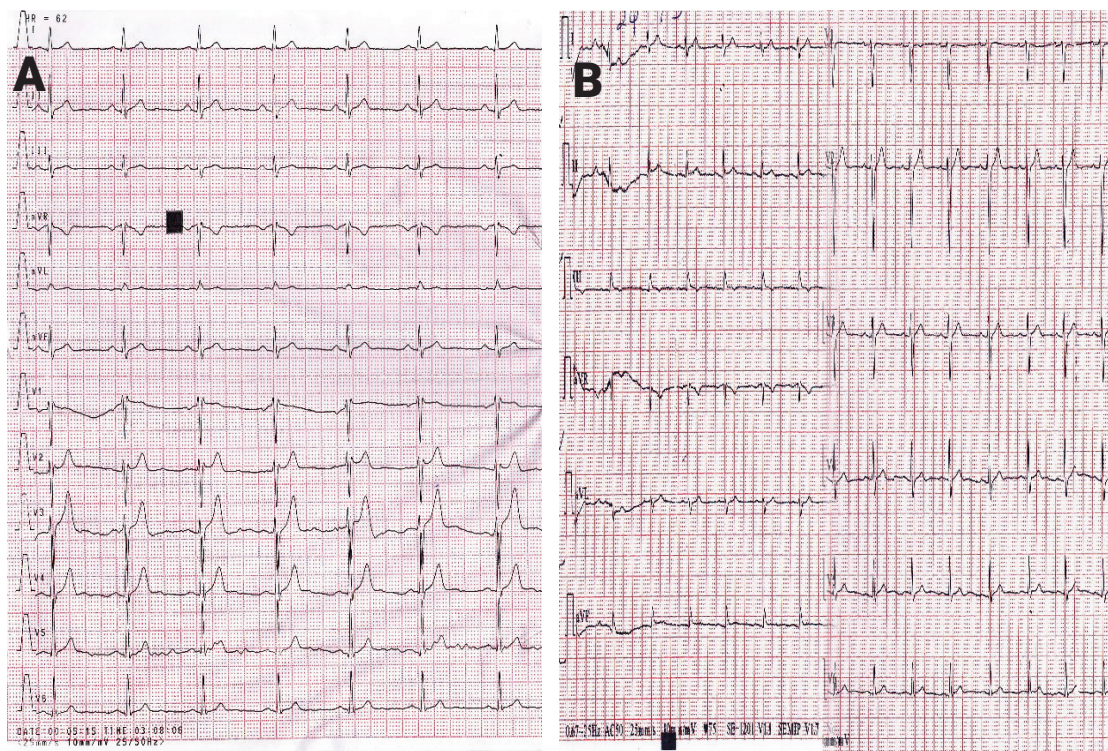


Figure 1. ECG alterations at the time of diagnosis. A (Case 1): Marginal ST-segment elevation in the inferior limb leads. B (Case 2): Abnormalities of the ST-segment (ST elevation) in the inferior limb and from septal to left precordial leads – sinus tachycardia

elevation in the inferior limb leads with no corresponding findings in the right and posterior precordial leads (Figure 1A). No fever was reported in the last days and his temperature was 36.8 C. His blood pressure was 117/78 mmHg, and his heart rate was 52 beats per minute. No shortness of breath was reported, and the oxygen saturation was up to 98%. The physical exam did not reveal any pathological findings, and no pericardial rub sound was auscultated. The chest X-ray showed a normal cardiothoracic ratio and physiological findings from the imaging of both lung fields.

The patient was admitted to the Coronary Intensive Care Unit (CICU) for monitoring. COVID-19 nasal swab testing using polymerase chain reaction was negative. The transthoracic echocardiogram (TTE) did not show any severe hypokinetic segments in the left ventricular myocardium, with the left ventricular ejection fraction (LVEF) estimated up to 60%. Laboratory blood tests confirmed the suspicion of myocardial injury. Troponin-T high sensitive (TnT-hs) was 0.096 ng/ml (optimal values <0.014 ng/ml), creatine phosphokinase (CPK) was 194 IU/L (normal range: 20-180 IU/L), and creatine phosphokinase myocardial band (CPK-MB) was 31 IU/L (normal range: <25 IU/L). C-reactive protein (CRP) was also elevated at 1.12 mg/dl (normal: <0.5 mg/dl) indicating Inflammation, whereas white blood cells (WBC) were counted normal at 8.59 (normal range: $4-11 \times 10^9/L$). The peak of the values was reached in the next 24 hours, with TnT-hs 0.348 ng/ml, CPK 323 IU/L, CPK-MB 48 IU/L, and CRP 2.21 mg/dl, respectively. Laboratory values then declined, while the patient was completely relieved from pain 16 hours afterward.

The patient was not taken for an emergent coronary angiogram since he was at a low clinical probability of having coronary heart disease, due to his young age and lack of family history, but also because of the absence of risk factors for atherosclerotic disease. TTE also ruled out the possibility of Takotsubo or any other cardiomyopathy. Myocarditis antibody panel test (for Coxsackie, Echovirus, Influenza, Chlamydia pneumoniae, Hepatitis B and C, Adenovirus, Enterovirus, Cytomegalovirus, and Epstein-Barr) was negative. A few days later, he underwent cardiac magnetic resonance imaging (MRI), which showed findings compatible with sub-epicardial fibrosis and myocardial edema and hyperemia due to recent myocarditis, with signs of late gadolinium enhancement (LGE) to the basal and medial posterior/inferior walls (Figure 2A).

The patient was discharged after a total of five days of hospitalization, with instructions for restriction of physical activity, as recommended after myocarditis. After four months of follow-up, the patient is completely asymptomatic with a satisfactory left ventricular performance.

Case 2 presentation

This is a case of a healthy 22-year-old man, non-smoker, without a history of cardiovascular disease or obesity (BMI 24.7 kg/m²). There was no known family history of cardiovascular or autoimmune disease. He arrives at the hospital due to the onset of chest discomfort, vomiting, and bilateral arm tightness during the last 15 hours. Six months before, he had been infected with SARS-CoV-2 and developed mild illness (weakness and headache without fever), with complete recovery without hospitalization. As he was an amateur runner, after his recovery

ery, he was examined by a cardiologist, and the echocardiogram showed an excellent cardiac performance with a LVEF > 60%. Seven days before the patient's arrival at the hospital, he had undergone the booster dose of the BNT162b2 mRNA vaccine, according to National Public Health Protocols. In the emergency department, ECG showed abnormalities of the ST segment in the inferior limb and from septal to left precordial leads. (Figure 1B) His body temperature was elevated at 37.6 degrees Celsius. His blood pressure was 128/84 mmHg, and his heart rate was 74 beats per minute. His oxygen saturation was up to 97%. The physical exam showed paleness and exhaustion, because of vomiting, while the chest X-ray did not show any significant pathological findings.

The patient was immediately admitted to the CICU. COVID-19 re-infection was ruled out by negative nasal swab testing using polymerase chain reaction. The TTE displayed mild segmental hypokinesis in the inferior and basal-lateral wall of the left ventricle, which presented satisfactory, though not excellent, overall systolic function, with an estimated LVEF of about 53%. Laboratory blood tests confirmed myocardial damage, with TnT-hs measured at 0.245 ng/ml, CPK at 382 IU/L, and CPK-MB at 67 IU/L. CRP was 4.61 mg/dl, while WBCs were elevated up to $14.68 \times 10^9/L$. Laboratory values followed a declining trend, while the patient was carefully administered intravenous hydration and analgesics with rapid improvement of his clinical picture.

As in the previous case, coronary angiography was not performed since the patient was very young without any predisposing factors that could make the presence of coronary artery disease likely. Furthermore, the diagnostic investigation ruled out the existence of any cardiomyopathy or a previous recent viral infection that could cause myocarditis. Cardiac MRI showed sub-epicardial LGE of the inferior/basal segment of the lateral wall and the basal segment of the inferior wall of the left ventricle (Figure 2B).

He was administered a small dose of per os beta-blocker (Bisoprolol 2.5 mg) and the patient was discharged after five days of hospitalization. Usual instructions were also given for limiting sports activities, as suggested, after myocarditis. One month later, his echocardiogram displayed an excellent left ventricular function, with an estimated LVEF >60%. After four months of follow-up, the patient remains completely asymptomatic.

4. DISCUSSION

The development of myocarditis after vaccination for COVID-19 is an uncommon side effect and is mainly related to mRNA vaccines. Its prevalence, as recently announced by the European Medicines Agency, is less than

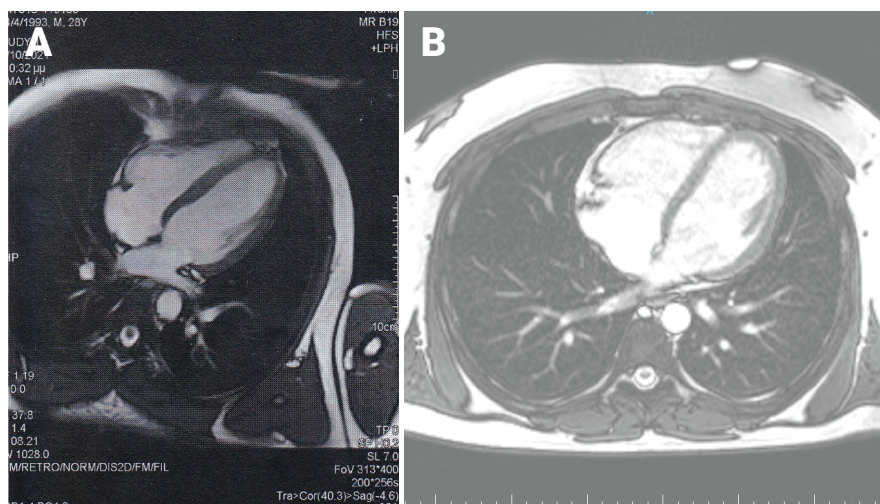


Figure 2. Cardiac Magnetic Resonance (CMR) images. Case 1 (A) and Case 2 (B) showing subepicardial late gadolinium enhancement to the basal and medial posterior/inferior walls consistent with myocarditis (arrows)

1 in every 10,000 vaccinated and mainly affects adolescents and young male adults. Myocarditis probability after SARS-CoV-2 infection in unvaccinated young people is at least six times higher than in vaccinated. Although the exact pathogenetic mechanism is still unknown, it is probably provoked either by an immune response or inflammation caused by the virus and, in particular, by the viral spike protein (3). Vaccine-associated myocarditis has been reported, too, after other vaccines such as influenza or tetanus (4, 5).

Myocarditis associated with SARS-CoV-2 vaccine-related vaccines usually causes mild symptoms and resolves quickly. The majority of myocarditis cases reported in the literature after COVID-19 vaccination involve the BNT162b2 and less the mRNA-1273 vaccine.

Regarding the presented cases, apart from the fact that both vaccines are with mRNA technology, which is a pioneering method in the field of vaccines, there are also several other similarities to be reported. Both patients, coincidentally or not, presented to our hospital during the same season time in the summer period. Moreover, both had negative COVID-19 nasal swab testing using polymerase chain reaction. Both diagnoses were based on the criteria for the definition of myocarditis, namely the presence of typical symptoms, with an increase of troponin levels, combined with cardiac MRI findings consistent with myocarditis and having ruled out other causes for their clinical manifestation (6). Patients' characteristics were similar: young men belonging to the age group 20-30 years old, non-smokers, non-obese, without any underlying cardiovascular or autoimmune comorbidity to require the administration of medication, and no medical family history. ECG was the first pathognomonic diagnostic test that raised the suspicion of the final diagnosis. In both cases, the physical examination did not reveal any specific pathological signs. Both presented with blood pressure, heart rate, and oxygen saturation within normal, and chest X-ray with normal findings. Both were admitted to the CICU for monitoring and discharged home after five days without presenting

Characteristics	Case 1	Case 2
Vaccine type	mRNA-1273	BNT162b2
Doses received	2	1
Prior COVID-19 infection	No	Yes
Sex	Male	Male
Age (years)	28	22
BMI (Kgr/m ²)	23.8	24.7
Comorbidities		
Risk factors for CAD ^(a)	No	No
Smoking	No	No
Prior history of CVD	No	No
Autoimmune disease	No	No
Prior myocarditis	No	No
Received medication until the vaccination	None	None
Clinical Picture		
Symptoms	Chest pain	Chest discomfort, vomiting, bilateral arm tightness
Days after vaccination	4	7
Fever (degrees Celsius)	No (36.8)	Yes (37.6)
Blood Pressure (mmHg)	117/78	128/84
Heart Rate (bpm)	52	74
Oxygen Saturation (%)	98	97
Physical Examination	Normal	Paleness, exhaustion
Pericardial rub sound	No	No
Diagnostic Investigation		
COVID-19 testing ^(b)	Negative	Negative
ECG	ST-elevation in II,III,avF	ST-elevation in II,III,avF,V3-V6
Chest X-ray	Normal	Normal
TnT-hs (ng/ml) ^(c)	0.348 (Abnormal)	0.245 (Abnormal)
CPK (IU/L) ^(c)	323 (Abnormal)	382 (Abnormal)
CPK-MB (IU/L) ^(c)	48 (Abnormal)	67 (Abnormal)
CRP (mg/dl) ^(c)	2.21 (Abnormal)	4.61 (Abnormal)
WBC (x10 ⁹ /L) ^(c)	8.59 (Normal)	14.68 (Abnormal)
Virus antibody panel test for myocarditis ^(d)	Negative	Negative
TTE	No severe hypokinesis, LVEF 60%	Mild segmental hypokinesis (inferior, basal-lateral), LVEF 53%
Coronary Angiography	NP	NP
Cardiac MRI	Sub-epicardial late gadolinium enhancement to the basal and medial posterior/inferior walls	Sub-epicardial late gadolinium enhancement of the inferior/basal segment of the lateral wall and the basal segment of the inferior wall of the left ventricle
Clinical Outcome		
Haemodynamic Stability	Yes	Yes
Arrhythmias	No	No
Specific Therapy ^(e)	None	None
Supportive Therapy	Analgesics	Analgesics, hydration, beta-blocker
Length of Hospital stay (days)	5	5
4-month follow-up	Asymptomatic	Asymptomatic

Table 1. Summary of data from both presented myocarditis cases, (a) Hypertension, Diabetes, Hypercholesterolaemia, Family history of Heart Disease, (b) Nasal swab testing using polymerase chain reaction, (c) Peak values, (d) Coxsackie, Echovirus, Influenza, Chlamydia pneumoniae, Hepatitis B and C, Adenovirus, Enterovirus, Cytomegalovirus, and Epstein-Barr, (e) NSAIDs, corticosteroids, colchicine

any sign of haemodynamic or electrical instability. In both, there was an increase of troponin and other cardiac biomarkers levels, but also of CRP indicating myocardial injury and inflammation, respectively. In both, the virus antibodies panel test was negative. Furthermore,

neither coronary angiography was considered reasonable to perform as the probability of coronary artery disease was extremely low, nor endomyocardial biopsy since patients' clinical stability did not justify any potential complication by the procedural risk given that our

SIMILARITIES	DIFFERENCES
Sex	Type of mRNA Vaccine
Age	Number of vaccine doses received
Body Mass Index	Prior COVID-19 infection
Absence of comorbidities	Clinical picture
Negative COVID-19 testing	Time of symptoms onset after vaccination
Normal Chest X-ray	Electrocardiographic findings
Kinetics of cardiac biomarkers	Echocardiographic findings
Negative virus antibody panel test	Magnetic resonance imaging findings
Good clinical outcome	

Table 2. Summary of similarities and differences between the two cases

treatment strategy did not need to be modified. In both cases, cardiac MRI showed at least one focal subepicardial lesion after gadolinium enhancement in non-ischaemic distribution, which is the most common myocarditis distributed lesion. Finally, they were given identical instructions for physical activity limitation, while during the four-month follow-up their ECG, and Echocardiogram were within normal, and they remained completely asymptomatic.

Regarding the small differentiations between the case of the mRNA-1273 vaccine and the BNT162b2 vaccine, the most important one concerns the temporal appearance of myocarditis during the vaccination process. That is, myocarditis of the first case occurred four days after the second dose of the mRNA-1273 vaccine, whereas in the second case emerged seven days after the booster dose of the BNT162b2 vaccine, in a patient who had already been infected with COVID-19 six months before. Furthermore, the electrocardiographic disorders of the first case were found only in the inferior limb leads, whereas in the second case, they were presented more diffuse, in the inferior limb leads and from the septal to the left precordial leads. Another difference was revealed with the 2-Dimensional Echocardiogram wherein, in the first case, no significant segmental left ventricular hypokinesis was observed, in contrast to the second one where mild ventricular hypokinesis was marked in the inferior and basal-lateral wall, maintaining, however, the LVEF above 50%. The above disorders were also depicted in cardiac MRI, wherein in the case of mRNA-1273 vaccine, the fibrosis was limited exclusively to the basal-mid inferior-posterior wall of the left ventricle, whereas in the case of the BNT162b2 vaccine, findings were more extensive, existing not only in the basal-inferior wall but also in the inferior-basal segment of the lateral wall. Noteworthy is the differentiation of the clinical picture in the emergency department, where low-grade fever occurred only in the case of the BNT162b2 vaccine and not the mRNA-1273 vaccine. Moreover, the laboratory blood tests fluctuations were slightly higher in the case of the BNT162b2 vaccine. Finally, in addition to the supportive treatment in the case of the BNT162b2 vaccine, a small dose of beta-blocker was administered due

to the marginally increased heart rate, something that was not considered necessary in the first case. All the above data are outlined in detail in Table 1.

In summary, comparing the two cases, although there are many similarities, features such as fever, the peak values of laboratory blood tests, the electrocardiographic detection of ST-segment disorders, the echocardiographic display of mild hypokinesis, but also the extent of fibrosis in cardiac MRI, indicate that the severity of myocarditis caused by the BNT162b2 vaccine was clinically higher than that of the mRNA-1273 vaccine, although both patients' hospitalization was uncomplicated (Table 2).

Our findings are consistent with recent data. First, the diagnosis was made according to the Centers for Disease Control and Prevention working case definitions for acute myocarditis, announced in June 2022 (6). Beyond the presence of at least one new clinical symptom (chest pain and discomfort, respectively) (7, 8), there were reported compatible with myocarditis cardiac MRI findings in combination with the presence of troponin levels above the upper limit of normal, excluding other identifiable causes of the symptoms and findings.

Further, both patients had the clinical picture and the outcome of the multitude of cases, like those demonstrated in a recent meta-analysis of the clinical presentation and outcomes of myocarditis post-mRNA-vaccination (9). According to this meta-analysis, the median patients' age is 21 years, and the majority of them are males (92.7%). As far as the type of vaccine, BNT162b2 is responsible for 76.8% of cases of myocarditis, while mRNA-1273 is responsible for 23.2% of them (10). In the vast majority, no significant history was reported (81.2%), while in a small percentage, myocarditis concerns patients who received post-COVID vaccination (8.7%) (11, 12). Most cases occurred after the second dose (88.4%) with an average appearance on the second day (range 0–4 days), while much fewer occurred after the first dose (11.6%) with an average appearance on the fourth day (range 2–25 days) (13). Chest pain/discomfort affects 100% of patients, fever is present at 44.9%, and vomiting at 8.7%. Regarding laboratory tests, TnT-hs is increased, with an average value of 0.70 ng/ml (range 0.18–15.34 ng/ml), as well as CRP in 92% of cases. Electrocardiographic disorders are observed in almost all patients, with ST-elevation reaching up to 78.8% of them. Concerning the Echocardiogram, LVEF >50% with no regional wall abnormalities is observed in 67.3% of cases, while hypokinesis in 29.1%. Cardiac MRI depicts specific findings in 100% of cases with mRNA vaccine-induced myocarditis (14–16). Specific anti-inflammatory therapy has been administered in 60.9% of the cases (our patients did not need this like the 39.1%), while the average length of hospital stay is four days (in our cases, the patients were hospitalized for five days), and they clinically completely recovered like the total number of patients recorded in the literature (17, 18).

All findings in the literature suggest that myocarditis after COVID-19 vaccination is usually mild and passes fast. The appearance of suspicious symptoms, especially

in the first days after vaccination, should be investigated, according to the protocols, to diagnose and treat the rare cases of this side effect. Under no circumstances should the occurrence of uncommon side effects affect the significance of vaccination as one of the weapons in the COVID-19 pandemic management. Further studies and vigilance are required to reveal the long-term effects of myocarditis in these patients.

5. CONCLUSION

The benefits of vaccination against COVID-19 outweigh possible untoward effects and especially myocarditis. Health workers must closely monitor the vaccinated patients for possible future cardiovascular complications.

- **Patient's Consent Form:** The study protocol was approved by the Scientific Committee of the Hospital (Number 12/2022) according to the Helsinki Declaration, and written consent was obtained from all patients. The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.
- **Author's contribution:** All authors were involved in all steps of the preparation of this article. Final proofreading was made by the first author.
- **Conflict of interest:** None declared.
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