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Myocardial infarction or myocarditis? A case report and review of a myocardial adverse event associated with mRNA vaccine

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A 23-year-old man started with chest pain 8 h after his first Pfizer-BioNTech COVID-19 vaccination. ECG evaluation showed sinus tachycardia with ST-segment elevation in D1, AVL, V5, and V6, the findings compatible with acute subepicardial myocardial damage. However, cardiac MRI documented myocardial fibrosis, with cardiac late enhancement non-ischemic pattern with diffuse edema. He had no other symptoms to suggest another etiology than the vaccination. The patient was hospitalized and received corticosteroid (prednisolone) daily. Then, 2 weeks after hospitalization, all laboratory parameters and ECG were normal and the patient was discharged from the hospital. The patient had a history of Wolf-Parkinson White that was corrected with ablation when he was 11 years old. This report calls attention to myocardial adverse reaction risk for mRNA COVID-19 vaccines for people with a previous cardiac disease history.

KEYWORDS

COVID-19, mRNA vaccine, cardiotoxicity, cardiac disease, adverse event

Introduction

Heart inflammation, such as endocarditis, myocarditis, and pericarditis, is the adverse reaction associated with mRNA vaccination reported in several countries during the COVID-19 vaccination development and after the onset of the vaccination campaign (1–6). Overall, six cases of myocarditis after the BNT162b2 vaccination were reported by Abu Mouch and Roguin et al. (1), with five patients presenting myocarditis after the second and one after the first dose of the vaccine. The six patients were men, with a median age of 23 years. Additional cases of myocarditis were also reported in individuals who received the Moderna mRNA COVID-19 vaccine (1). In adolescents and young adults, the reports of myocarditis and pericarditis were higher in frequency after the second dose than the first dose of one mRNA COVID-19 vaccine (Pfizer-BioNTech or Moderna) (1, 4, 6).

Overall, a review by the Centers for Disease Control and Prevention (CDC) of the Vaccine Adverse Events Reporting System (VAERS) identified a total of 1,226 cases of myocarditis as of 11 June 2021 (4). From 29 December 2020 to 11 June 2021, about 296 million doses of mRNA COVID-19 vaccines were administered in the USA, being 52 million to persons aged 12–29 years, receiving 30 and 22 million as first and second doses, respectively (4). The cases reported using the electronic VAERS CDC reporting system should be carefully evaluated (7), since a report to VAERS does not mean that a vaccine caused a myocardial adverse event, which should fit the diagnostic criteria for myocarditis, following the classification of the Brighton Collaboration (8). The revision of myocarditis cases reported to VAERS by the cardiologists in persons aged below 30 years reported from 1 May to 11 June 2021, and 323 cases (among 484 records) met the CDC criteria in case definitions for myocarditis, myopericarditis, or pericarditis (4).

Recently, a retrospective review of data from 5,125,696 Israeli residents which received two doses of the BNT162b2 mRNA vaccine (Pfizer-BioNTech) showed 283 having definitive or probable myocarditis attributed to the vaccination among 304 reported cases, including one fulminant fatal case (9). However, in most cases (95%—129 recipients), the myocarditis was mild, occurring in 142 persons after the first dose or a month following the second dose. In another report from Israel, the authors estimated an incidence of myocarditis of 2.13 cases/100,000 persons who had received at least one dose of vaccine [95% confidence interval (CI), 1.56–2.70], and the highest incidence (10.69 cases per 100,000 persons; 95% CI, 6.93–14.46) was reported in young male patients (aged between 16 and 29 years) (10).

The occurrence of myocarditis associated with the mRNA vaccine, on an overall risk difference between the first and second doses, has been estimated as 1.76 per 100,000 persons [95% confidence interval (CI), 1.33–2.19], with the most considerable difference among male aged between 16 and 19 years (difference, 13.73 per 100,000 persons; 95% CI, 8.11–19.46) (4, 10, 11).

In this report, we call the attention of public health services to include an advertisement for individual selection of COVID-19 type of vaccine for persons with a history of previous cardiac diseases.

Case description

A 23-year-old man presented with oppressive chest pain that started 6–8 h after being administered with his first Pfizer-BioNTech COVID vaccination dose. His initial vital signs were a temperature of 38.7^{o}C, blood pressure of 130/70 mmHg, heart rate of 128 bmp, and 100% oxygen saturation at the emergency room. The initial levels of cardiac enzymes evaluated were troponin $I > 15$ ng/ml ($N = 0.04$ ng/ml), CK = 1,894 U/L ($N = 294$ U/L), and CK-MB = 65.74 ng/ml ($N = 5.0$ ng/ml). Troponin I and CK-MB levels dropped to normal values 5 days later (**Table 1**).

The electrocardiogram (ECG) 8 h after BNT162b2 messenger RNA (mRNA) vaccine (Pfizer-BioNTech) administration on 15 August 2021 showed sinus tachycardia with ST-segment elevation in D1, AVL, V5, and V6, abnormalities compatible with acute subepicardial myocardial infarction (LV) left ventricular lateral wall (LV) (**Figure 1A**), whereas the ECG was normalized 13 days after vaccination (**Figure 1B**).

His echocardiogram with the Doppler findings at admission was a mild-to-moderate left ventricular dysfunction associated with mild pericardial effusion with a left ventricular ejection fraction of 56% and, at discharge, was 65%. Nevertheless, the cardiac magnetic resonance image (**Figure 2**) documented myocardial non-ischemic fibrosis 5 days later, with a cardiac enhancement non-ischemic pattern with diffuse edema. During the hospitalization, the patient received corticosteroid (prednisolone) on the following schedule: 120 mg for 3 days, 60 mg for 3 days, and 30 and 20 mg until visiting the doctor of infectious disease (ID). Then 2 weeks after hospitalization, all laboratory parameters and ECG were normal. The patient was discharged from the hospital, and during the visit to the ID doctor, the steroid therapy was suspended after performing a new ECG, which gave a normal result.

Additional evaluations by computerized tomography of the chest showed no evidence of pulmonary embolism or any identifiable pathology. The patient was not under stress, did not consume a significant amount of caffeine, and denied using any drugs or taking any over-the-counter medications (including herbals or supplements). He had no additional symptoms indicative of possible causes for the myocarditis other than the vaccine taken. He has a familiar history of Wolf-Parkinson White syndrome which was corrected with ablation when he was 11 years old. Moreover, he had a documented myocarditis of unknown cause 8 years previous to this episode. His father died of a sudden cardiac attack at the age of 50 years. A timeline of events is presented in **Figure 3**.

Discussion

The SARS-CoV-2 vaccination disrupted the COVID-19 pandemic. An estimated 3.6 billion (47.6%) people in the world had received at least one dose of the COVID-19 vaccine, and the number of global COVID-19 cases and deaths dropped to less than 10% in developed countries, whereas overall, at least 40% of the population were vaccinated. In contrast, only 2.5% of people in low-income countries received at least one dose of vaccine (12). Unquestionable is the benefit of COVID-19 vaccination. By 9 October 2021, the world data reported that SARS-CoV-2S-based mRNA vaccine types were administered to 233.39 million people for the Pfizer-BioNTech and 152.84 million for the Moderna vaccine. This type of vaccine is indicated for frail patients, such as those with autoimmune diseases, transplant recipients, and patients living with HIV since they showed higher efficacy and higher estimated effectiveness (13–15). Thus, knowing predisposition factors that could determine the development of severe cardiac adverse events upon mRNA vaccination is of great relevance for vaccination programs.

Overall, solicited systemic adverse events were reported during the trials for dose definitions of the Moderna vaccine (16). The adverse reaction to this mRNA vaccine, such as local adverse events, which were nearly all mild or moderate, and pain at the injection site, was most frequently reported with a higher dose and, more frequently, after the second dose. Solicited systemic and local adverse events occurred in most adults and adolescents across both vaccinations with the Pfizer-BioNTech mRNA vaccine, including high fever, fatigue, chills, headache, myalgia, and pain at the injection site (16, 17). Among the recipients of the Pfizer-BioNTech, four serious adverse events related to the vaccine were reported (shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and

TABLE 1 Laboratory results of cardiac enzymes.

		Date of examination					
Examination	Ref. value	08/15/2021 10:00 PM	08/16/2021 02:00 AM	08/17/2021 05:00 AM	08/18/2021 05:00 AM	08/19/2021 06:00 AM	08/20/2021 06:00 AM
CPK	294 U/L	121.25	121.25	121.25	121.25	121.25	121.26
CK-MB	0.03 ng/ml	47.73	65.76	10.14	2.30	2.08	1.17
Troponin I	0.03 ng/ml	> 15	14.42	8.24	3.54	1.08	0.18

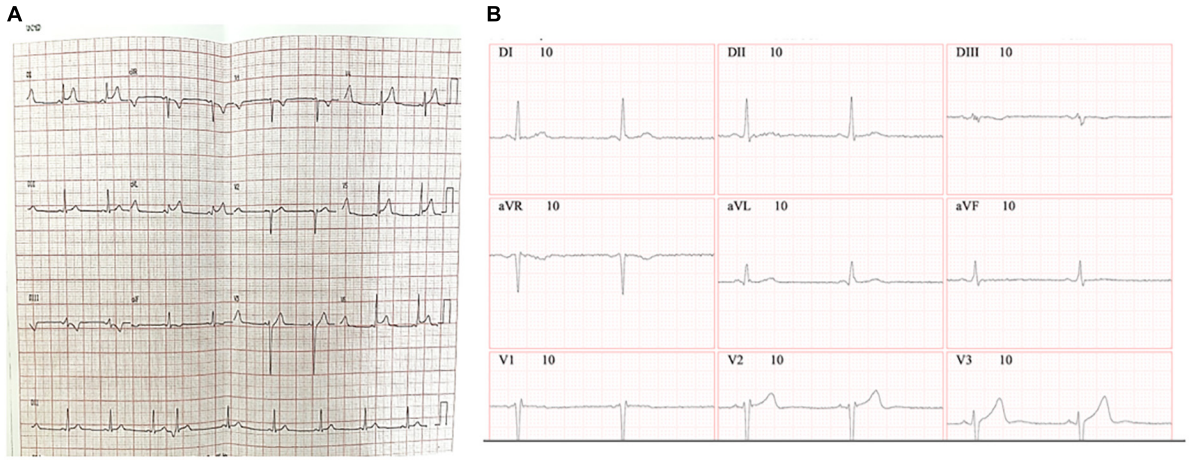

FIGURE 1
Electrocardiogram results. ECG was recorded with a set of 12-lead ECG electrodes connected to a central unit software. ECG was taken 8 h **(A)** or 13 days **(B)** after the administration of the BNT162b2 messenger RNA (mRNA) (Pfizer-BioNTech) vaccine.

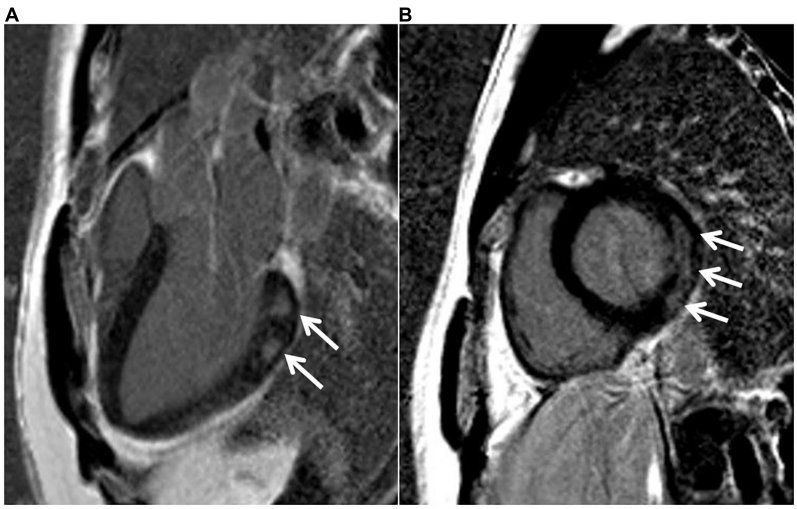

FIGURE 2
MRI results. Cardiac MRI 16 days after the administration of the BNT162b2 messenger RNA (mRNA) (Pfizer-BioNTech) vaccine, 1.5-T MR system. Delayed enhancement sequence in the long axis **(A)** and short axis **(B)**. Arrows indicate an area of myocardial fibrosis with a non-ischemic pattern in the basal lateral wall, compatible with myocarditis.

right leg paresthesia). Myocarditis is unquestionably a serious adverse reaction and, following mRNA vaccination, it is estimated to occur, following a second dose, at a rate of 12.6–24 cases per million, more often in adolescents and young adults at the age of 18–29 years (10, 11).

In total, two persons vaccinated with BNT162b2 died in the phase 2/3 study, one due to arteriosclerosis, and the other, by cardiac arrest (18). In another study, histopathological analysis in heart samples obtained from an autopsy of 25 individuals who were vaccinated with the mRNA vaccine for COVID-19 showed the presence of acute myocarditis with focal inflammatory foci in four persons without any signs of other possible causes of death (19). Previous cardiac diseases associated with cardiovascular adverse events were not related to the recipient's age of the mRNA vaccine. Our patient is a young

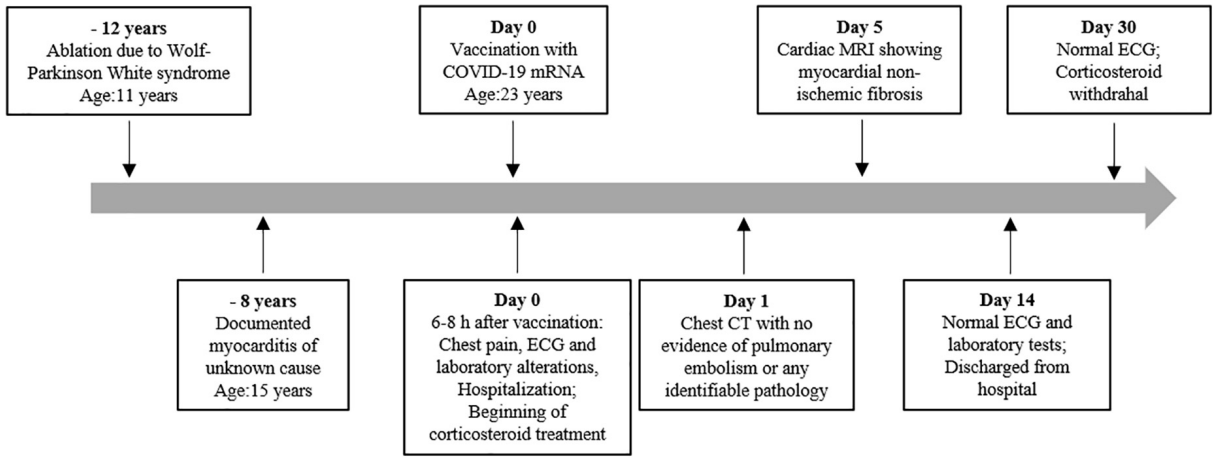

FIGURE 3
Timeline of the patient's previous cardiac diseases, myocarditis, and pericarditis post-BNT162b2 messenger RNA (mRNA) (Pfizer-BioNTech) vaccine.

TABLE 2 Reports on cardiotoxicity of SARS-CoV2 mRNA vaccines.

References	Vaccine	Number of cases	Manifestation	Country
Abu Mouch et al. (1)	BNT162b2	6	Myocarditis established by cardiac MRI	Israel
D'Angelo et al. (2)	BNT162b2	1	Myopericarditis by laboratory and cardiac MRI	Italy
Deb et al. (3)	mRNA-1273	1	Myocarditis	USA
Gargano et al. (4)	BNT162b2 and mRNA-1273	323 confirmed of 484 < 30 years	Myocarditis, pericarditis, myopericarditis confirmed by revision of cases	USA
Khogali and Abdelrahman (5)	mRNA-1273	1	Acute perimyocarditis	Qatar
Mevorach et al. (9)	BNT162b2	136	Myocarditis (definitive or probable)	Israel
Witberg et al. (10)	BNT162b2	54	Myocarditis	Israel
Larson et al. (26)	BNT162b2 and mRNA-1273	8	Myocarditis by laboratory and cardiac MRI	USA and Italy
Marshall et al. (27)	BNT162b2	7	Acute myocarditis or myopericarditis	USA
Verma et al. (28)	BNT162b2 and mRNA-1273	2	Myocarditis	USA
Freise et al. (29)	BNT162b2 and mRNA-1273	8	Cardiac symptoms compatible with myocarditis	Germany
Meier et al. (30)	BNT162b2 and mRNA-1273	1	Subclinical pericarditis established by cardiac MRI	Germany
Saadi et al. (31)	BNT162b2	1	Myocarditis	Saudi Arabia
Kim et al. (32)	BNT162b2 and mRNA-1273	4	Myocarditis by laboratory and cardiac MRI	USA
Montgomery et al. (33)	BNT162b2 and mRNA-1273	21	Myocarditis by laboratory and cardiac MRI	USA
Schwab et al. (19)	BNT162b2 and mRNA-1273	4	Acute (epi-) myocarditis by histopathological analysis	Germany
Schneider et al. (34)	BNT162b2	1	Myocarditis	Germany

adult with previous history of cardiac arrhythmia and presented a myocarditis simulating myocardial infarction event. His ventricular dysfunction, cardiac enzyme elevations, and ECG suggested acute subepicardial myocardial infarction, which the cardiac MRI could not confirm. However, transient myocardial non-ischemia fibrosis without necrotic consequences could be shown by cardiac MRI. Moreover, myopericarditis can be associated with atrioventricular (AV) dissociation, a condition of desynchrony of electrical activity between atria and ventricles associated with ST elevation in the anterior, leading to the altered ECG and raised troponin I levels (20, 21). One limitation of this case investigation was the lack of coronary angiography, which could help to rule out myocardial infarction.

The presence of histological changes compatible with myopericarditis was shown in an experimental study after the first priming dose by intravenous route in mice. The myopericarditis persisted for 2 weeks and was aggravated by a second booster dose by intramuscular or intravenous routes (22). In addition, the gene expression of pro-inflammatory cytokines such as IL-1β, IFN-β, IL-6, and TNF-α in the hearts was significantly increased after the mRNA vaccine injection by intravenous route. Lipid nanoparticles are the most commonly utilized carriers for *in vivo* RNA delivery due to their ability to protect mRNA molecules from degradation, bring mRNA to the negatively charged cell membranes, and mediate endocytosis and endosomal escape (23, 24).

Indeed, there is no doubt that mRNA vaccines affect myocardial cells, possibly by inducing and increase in IL-18 levels (25). The CDC surveillance committee for COVID-19 vaccine adverse reactions previously recommended a precaution for the administered mRNA-based vaccine (7). **Table 2** summarizes the studies describing the cardiotoxicity of SARS-CoV-2 mRNA vaccination. Importantly, a systematic literature review highlights that protective immune responses elicited by COVID-19 mRNA vaccines decline within 90–180 days, indicating the need to continuously boost the population (35).

We conclude that, even though the mRNA COVID-19 vaccine appears to be very safe, a careful selection of the type of COVID-19 vaccine should be done for young males with a history of cardiac disease. Additionally, chest pain with ECG alteration suggests myocarditis in patients that report being vaccinated with the mRNA COVID-19 vaccine may not necessarily be cardiac ischemic disease.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of SENAI CIMATEC. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

RB, GN, AA, and CA conducted the diagnostics and medical assistance. RB wrote the original draft. BM, JB, and MS edited and contributed to the literature quoted in this manuscript. All authors read and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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