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Myocarditis after BNT162b2 and mRNA-1273 Vaccination

Running Title: *Larson & Ammirati, et al.; Myocarditis and BNT162b2, mRNA-1273 Vaccinations*

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The BNT162b2 mRNA (Pfizer-BioNTech) and the mRNA-1273 (Moderna) COVID-19 vaccines have gained widespread use across the globe to prevent further severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection spread. Early studies and surveillance data suggest these vaccines are associated with no significant adverse events other than very rare anaphylaxis.[1,2] Surveillance for other reactions continues.

Myocarditis and inflammatory myocardial cellular infiltrate have been reported after vaccination, especially after the smallpox vaccine.[3] Nevertheless, myocarditis occurring after the BNT162b2 mRNA and mRNA-1273 vaccines has not been reported in trials.[1,2] Here, we describe 8 patients hospitalized with chest pain who were diagnosed with myocarditis by laboratory and cardiac magnetic resonance imaging (MRI) within 2-4 days of receiving either the BNT162b2 or mRNA-1273 vaccine (**Table 1**). Patients provided written informed consent, and the collection of clinical cases followed local Institutional Review Boards. The data that support the findings of this study are available from the corresponding author upon reasonable request. Two of the patients (3 and 4) had previously been infected by SARS-CoV-2 without need for hospitalization. All individuals were otherwise healthy males between the ages of 21 and 56. All but one patient developed symptoms after their second dose. Systemic symptoms began within 24 hours after vaccine administration in 5 out of 8 patients, with chest pain presenting between 48 and 96 hours later. Chest pain was most commonly described as constant, non-positional, and non-pleuritic (only patient 7 reported pericardial pain), consistent with acute myocarditis mainly without pericardial involvement. Troponin values were elevated in all individuals and appeared to peak the day after admission, whereas none had eosinophilia. All patients were tested for and were negative for SARS-CoV-2. Left ventricular ejection fraction (LVEF) was reduced (<50%) in 2 of 8 (25%) patients with a median LVEF of 51.5% (first to third quartile: 48 to 59%). Five

patients demonstrated regional wall motion abnormalities with inferior and infero-lateral walls involved, and the remaining 3 cases had generalized hypokinesis. Some patients were tachycardic at presentation, but no patients required inotropes or mechanical circulatory support. All but three patients (1, 2, and 5) underwent coronary imaging by computed tomography or catheter-based angiography to rule out coronary artery disease. Cardiac MRI revealed patchy delayed gadolinium enhancement consistent with myocarditis in all patients, and most patients also demonstrated findings consistent with myocardial edema. Cardiac biopsy, performed in one of the patients before initiation of steroid, did not demonstrate myocardial infiltrate. All patients had resolution of their chest pain, were discharged from the hospital in stable condition, and were alive with preserved LVEF at last contact.

The patients presented here demonstrated typical signs, symptoms, and diagnostic features of acute myocarditis. The temporal association between receiving an mRNA-based COVID-19 vaccine and the development of myocarditis is notable. Trials that tested the BNT162b2 and mRNA-1273 vaccines showed that systemic reactogenicity more often occurred after dose 2 and generally within 48 hours after vaccination.[1, 2] On average, our patients presented with symptoms of acute myocarditis 3 days after the second injection, and in 5 out of 8 patients fever appeared a day before, supporting the hypothesis that myocarditis could be an mRNA-vaccine related adverse reaction. The only patient who experienced myocarditis after the first vaccination had a previous infection to SARS-COV-2. No eosinophilia was noted in our patients, unlike myocarditis associated with Smallpox vaccination.[3,4] Potential mechanisms for myocarditis post-mRNA-based vaccination include a non-specific innate inflammatory response or a molecular mimicry mechanism between viral spike protein and an unknown cardiac protein.[5] With regard to therapy, 3 patients received nonsteroidal anti-inflammatory drugs, 2 colchicine, 2

prednisone, and 3 received no medications. We would consider the use of corticosteroids in fulminant myocarditis due to the likely immune-mediated post-vaccination mechanism.[4] However, corticosteroids could reduce the specific immune response against SARS-COV-2 triggered by the vaccine. Thus, the duration of corticosteroid administration should be limited to the resolution of the symptoms or ventricular arrhythmias or the recovery of the LVEF. Pending publication of long-term outcome data after SARS-CoV-2 vaccine-related myocarditis, we suggest adherence to the current consensus recommendation to abstain from competitive sports for a period of 3-6 months with re-evaluation prior to sports participation.[4] As a case report collection, the current research letter emphasizes the real incidence of acute myocarditis after mRNA COVID-19 vaccine, which appears to be extremely rare. In fact, the Centers for Disease Control Vaccine Adverse Event Reporting System (www.wonder.cdc.gov/vaers.html), received reports of chest pain in 5166 and myocarditis in 399 recipients of the BNT162b2 or mRNA-1273 vaccine, whereas more than 129 million individuals have been fully vaccinated with these two vaccines. In conclusion, providers should be vigilant for myocarditis after COVID-19 mRNA vaccination; further research is required to understand the long-term cardiovascular risks.

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Disclosures

None

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Table 1. Patient demographics

Patient		Vaccine received	Day of presentation	Presenting symptom(s)	Baseline troponin*	Peak troponin*	CRP*	ECG	Lowest left ventricular ejection fraction	MRI findings	Anti-inflammatory Treatment	Clinical course
1	22 y male Caucasian (US)	mRNA-1273	3 days after 2nd dose	Fever, chills, myalgia on day +1, followed by chest pain day +3	104	285	4.8	Diffuse ST-segment elevation with depression in aVR	50%, generalized hypokinesis	Patchy subepicardial delayed enhancement	NSAIDs, prednisone	Hemodynamically stable, no clinical of heart failure. Intermittent chest pain resolved with ibuprofen and steroids.
2	31 y male, Caucasian (US)	mRNA-1273	3 days after 2nd dose	Fever, chills, myalgia on day +1, chest pain, shortness of breath on day +3	39.5	46	14	Normal ECG	34%, generalized hypokinesis	Patchy subepicardial and midmyocardial delayed enhancement	No	Hemodynamically stable, no clinical heart failure. Chest pain resolved with acetaminophen. Follow-up echocardiogram on day +11 with normal left ventricular function.
3	40 y male, Caucasian (US)	BNT162b2	2 days after 1st dose	Chest pain	102	520	9.5	Diffuse ST-segment elevation with depression in aVR, V1	47%, generalized hypokinesis	Edema, delayed enhancement, pericardial effusion	Prednisone, colchicine	Hemodynamically stable. Endomyocardial biopsy found no active myocarditis.
4	56 y male, Caucasian (Italy)	BNT162b2	3 days after 2nd dose	Chest pain	21	37	5.8	Diffuse peaked T waves	60%, inferolateral hypokinesis	Edema, delayed enhancement	No	Hemodynamically stable.
5	26 y male, Caucasian (Italy)	BNT162b2	3 days after 2nd dose	Cough, fever on day +1, chest pain on day +3	11	100	1	Inferolateral ST elevation	60%, inferior wall hypokinesis	Edema, delayed enhancement, pericardial effusion	Colchicine	2 days in intensive care, no inotropes or mechanical circulatory support. Discharged stable.
6	35 y male, Caucasian (Italy)	BNT162b2	2 days after 2nd dose	Fever on day +1, chest pain on day +2	18	29	9	Diffuse ST-segment elevation with depression in aVR	50%, lateral and inferolateral hypokinesis	Edema, delayed enhancement	NSAIDs	4 days in intensive care, no inotropes or mechanical circulatory support. Discharged stable.
7	21 y male, Caucasian (Italy)	BNT162b2	4 days after 2nd dose	Fever on day +1, chest pain on day +4	1.4	1164	4.6	Diffuse ST-segment elevation	54%, inferior and posterolateral hypokinesis	Edema, delayed enhancement, pericardial effusion, pericardial edema	NSAIDs	2 days in intensive care, no inotropes or mechanical circulatory support. NSVT episode. Discharged stable.
8	22 y male, Asian (US)	mRNA-1273	2 days after 2nd dose	Chest pain on day +2	1327	1433	4	Inferior, anterolateral ST-elevation	53%, inferolateral hypokinesis	Edema, delayed enhancement	No	NSVT episodes (N=3). Discharged stable.

*Values are expressed as the multiple of the upper limit of normal for each laboratory's reference range.
CRP indicates C-reactive protein; NSVT, non-sustained ventricular tachycardia.