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Myocarditis After BNT162b2 and mRNA-1273 Vaccination

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The BNT162b2 mRNA (Pfizer-BioNTech) and mRNA-1273 (Moderna) coronavirus disease 2019 (COVID-19) vaccines have gained widespread use across the globe to prevent further spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. 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] However, myocarditis occurring after the BNT162b2 mRNA and mRNA-1273 vaccines has not been reported in trials.[1,2] Here, we describe 8 patients who were hospitalized with chest pain and who were diagnosed with myocarditis by laboratory and cardiac magnetic resonance imaging within 2 to 4 days of receiving either the BNT162b2 or mRNA-1273 vaccine (Table). Patients provided written informed consent, and the collection of clinical cases followed local Institutional Review Board requirements. The data that support the findings of this study are available from the corresponding author on reasonable request. Two of the patients (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 years. All but 1 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, nonpositional, and nonpleuritic (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 no patient had eosinophilia. All patients were tested and were negative for SARS-CoV-2. Left ventricular ejection fraction was reduced (<50%) in 2 of 8 (25%) patients with a median left ventricular ejection fraction of 51.5% (first to third quartile, 48% to 59%). Five patients demonstrated regional wall motion abnormalities with inferior and inferolateral 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 3 patients (patients 1, 2, and 5) underwent coronary imaging by computed tomography or catheter-based angiography to rule out coronary artery disease. Cardiac magnetic resonance imaging 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 1 of the patients before steroid initiation, 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 left ventricular ejection fraction at last contact.

The patients presented here demonstrated typical signs, symptoms, and diagnostic features of acute

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Table 1. Patient Demographics

Patient		Vaccine received	Day of presentation	Presenting symptoms	Baseline troponin*	Peak troponin*	CRP*	ECG	Lowest left ventricular ejection fraction	MRI findings	Anti-inflammatory treatment	Clinical course
1	22 y; male; White (United States)	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; White (United States)	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; White (United States)	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; White (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; White (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; White (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; White (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 (United States)	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

CRP indicates C-reactive protein; NSAID, nonsteroidal anti-inflammatory drug; and NSVT, nonsustained ventricular tachycardia.
*Values are expressed as the multiple of the upper limit of normal for each laboratory's reference range.

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 vaccina-

tion.[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 SARS-CoV-2 infection. No eosinophilia was noted in our patients, unlike myocarditis associated with smallpox vaccination.[3,4] Potential mechanisms for myocarditis after mRNA-based vaccination include a nonspecific 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 NSAIDs, 2 received colchicine, 2 received prednisone, and 3 received no medications. We would consider the use of corticosteroids in fulminant myocarditis because of the likely immune-mediated postvaccination mechanism[4]; however, corticosteroids could reduce the specific immune response against SARS-CoV-2 that is triggered by the vaccine. Therefore, the duration of corticosteroid administration should be limited to the resolution of the symptoms or ventricular arrhythmias or the recovery of the left ventricular ejection fraction. 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 to 6 months with re-evaluation before sports participation.[4] As a case report collection, the current research letter emphasizes the real incidence of acute myocarditis after COVID-19 mRNA vaccination, which appears to be extremely rare. In fact, the Centers for Disease Control's Vaccine Adverse Event Reporting System (www.wonder.cdc.gov/vaers.html) received reports of chest pain and myocarditis in 5166 and 399 recipients, respectively, of the BNT162b2 or mRNA-1273 vaccine, whereas more than 129 million people have been fully vaccinated with these 2 vaccines. In conclusion, providers should be vigilant for myocarditis after COVID-19 mRNA vaccination, and further research is required to understand the long-term cardiovascular risks.

ARTICLE INFORMATION

The data that support the findings of this study and research materials, as well as experimental procedures and protocols, are available from the corresponding author upon reasonable request.

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REFERENCES

1. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, et al; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med.* 2021;384:403–416. doi: 10.1056/NEJMoa2035389
2. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, et al; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med.* 2020;383:2603–2615. doi: 10.1056/NEJMoa2034577
3. Engler RJ, Nelson MR, Collins LC Jr, Spooner C, Hemann BA, Gibbs BT, Atwood JE, Howard RS, Chang AS, Cruser DL, et al. A prospective study of the incidence of myocarditis/pericarditis and new onset cardiac symptoms following smallpox and influenza vaccination. *PLoS One.* 2015;10:e0118283. doi: 10.1371/journal.pone.0118283
4. Ammirati E, Frigerio M, Adler ED, Basso C, Birnie DH, Brambatti M, Friedrich MG, Klingel K, Lehtonen J, Moslehi JJ, et al. Management of acute myocarditis and chronic inflammatory cardiomyopathy: an expert consensus document. *Circ Heart Fail.* 2020;13:e007405. doi: 10.1161/CIRCHEARTFAILURE.120.007405
5. Segal Y, Shoenfeld Y. Vaccine-induced autoimmunity: the role of molecular mimicry an immune cross reaction, *Cell Mol. Immunol.* 2018;15:586-594. doi: 10.1038/cmi.2017.151