Circulation

RESEARCH LETTER

Myocarditis Temporally Associated With COVID-19 Vaccination

Carolyn M. Rosner, MSN, NP-C, MBA; Leonard Genovese, MD; Behnam N. Tehrani, MD; Melany Atkins, MD, MRMD; Hooman Bakhshi, MD; Saquib Chaudhri, MD, MBA; Abdulla A. Damluji, MD, PhD, MPH; James A. de Lemos, MD; Shashank S. Desai, MD, MBA; Abbas Emaminia, MD; Michael Casey Flanagan, MD; Amit Khera, MD; Alireza Maghsoudi, MD; Girum Mekonnen, MD, MPH; Alagarraju Muthukumar, MD; Ibrahim M. Saeed, MD; Matthew W. Sherwood, MD; Shashank S. Sinha, MD, MSc; Christopher M. O'Connor, MD; Christopher R. deFilippi, MD

The global coronavirus disease 2019 (COVID-19) pandemic brought significant mortality with more than 3 million deaths worldwide since January 2020.[1] Concerted efforts focused on the time-sensitive development of vaccines yielded 3 COVID-19 vaccines receiving provisional US Food and Drug Administration approval: Pfizer-BioNTech COVID-19 (BNT162b2; Pfizer, Inc; Philadelphia, PA), Moderna (mRNA-1273; ModernaTX, Inc; Cambridge, MA), and Janssen (Ad.26.COV2.S; Johnson and Johnson; New Brunswick, NJ).[1] All vaccines demonstrated excellent safety and clinical efficacy profiles in clinical trials. As of June 5, 2021, more than 170 million individuals in the United States and 894 million individuals worldwide had received at least 1 dose of a COVID-19 vaccine. Notwithstanding isolated rare serious adverse events, they have been well tolerated and associated with decreasing burden of disease in areas with high vaccination rates.[2]

Myopericarditis has been reported as a rare vaccination complication.[3] We present a case series of 7 patients hospitalized for acute myocarditis-like illness after COVID-19 vaccination, from 2 US medical centers in Falls Church, VA, and Dallas, TX. All were men <40 years of age and of White or Hispanic race/ethnicity (Table). Only 1 patient reported previous history of COVID-19 infection. Six patients received an mRNA vaccine (Moderna or Pfizer/BioNTech), and 1 received the adenovirus vaccine (Johnson and Johnson). All patients presented 3 to 7 days after vaccination with acute onset chest pain and biochemical evidence of myocardial injury, by cTnI ([cardiac troponin I]; Abbott Diagnostics, Lake Forest, IL) (mean peak, 15.77 ng/mL; median peak, 12.01 ng/mL) or elevated high-sensitivity cTnI (Abbott Diagnostics) (peak, 7000 ng/L). All were hemodynamically stable and none had a pericardial friction rub or rash. ECG patterns varied from normal to ST segment elevation. Three patients underwent invasive coronary angiography, and none had evidence of obstructive coronary artery disease. Echocardiograms showed left ventricular ejection fraction ranging from 35% to 62%, with 5 of 7 having some degree of hypokinesis. Patients underwent cardiac magnetic resonance imaging between 3 and 37 days after vaccination, including multiplanar SSFP sequences, short axis T1 and T2 stacks, T1 mapping when available and multiplanar myocardial late gadolinium enhancement. Multifocal subepicardial late gadolinium enhancement was present in 7 of 7 patients and additional midmyocardial late gadolinium enhancement was 4 of 7 patients. There was corresponding myocardial edema in 3 of 7 patients. Two patients who underwent cardiac magnetic resonance imaging >7 days from presentation had no edema, with an additional patient's T2 images limited by artifact. One patient underwent endomyocardial biopsy without pathological evidence of myocarditis. No patients reported palpitations, and there was no evidence of sustained arrhythmias. No patients had evidence of an active viral illness or autoimmune disease, and 6 of 7 had polymerase chain reaction testing for acute COVID-19 infection during hospitalization (all 6 were negative). Assessment of COVID-19 serology was obtained for 6 of 7 patients, with 4 of 6 showing presence of spike protein IgG antibodies.

Key Words: COVID-19 ■ COVID-19 vaccines ■ myocarditis

Correspondence to: Christopher deFilippi, MD, Inova Heart and Vascular Institute, Inova Fairfax Medical Campus, 3300 Gallows Road, Falls Church, VA 22042. Email christopher.defilippi@inova.org

This manuscript was sent to Vera Bittner, Senior Guest Editor, for review by expert referees, editorial decision, and final disposition.

The podcast and transcript are available as a Data Supplement at https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.121.055891.

For Sources of Funding and Disclosures, see page 503.

Circulation is available at www.ahajournals.org/journal/circ

Nonstandard Abbreviations and Acronyms

COVID-19	coronavirus disease 2019
cTnI	cardiac troponin I

Treatment varied and included β-blocker and anti-inflammatory medication. Hospital length of stay was 3±1 days, and all patients' symptoms resolved by hospital discharge. All cases were reported to the Vaccine Adverse Event Reporting System and the Centers for Disease Control. Institutional review board approval was obtained for this report. The data that support the findings of this study are available from the corresponding author on reasonable request.

In 1990, the United States established the Vaccine Adverse Event Reporting System and from 1990 to 2018, myopericarditis comprised 0.1% of all adverse events reported.[3] To date, while anecdotes of potential myocarditis from COVID-19 vaccines have been reported in the lay media[4] and the US Centers for Disease Control and Prevention has acknowledged investigation of potential cases, to our knowledge there are no reported case series of myocarditis-like illness associated with COVID-19 vaccination in adults. Our series of 7 male COVID-19 vaccination recipients who presented with myocarditis-like illness supports a potential causal association with vaccination given the temporal relationship, clinical presentation, and cardiac magnetic resonance imaging findings. Although endomyocardial biopsy was negative in the single case in which it was performed, this may represent sampling bias, given the patchy nature of myocardial inflammation in myocarditis.[5] Of the 2 patients without measurable spike protein IgG, both presented shortly after their first vaccine dose. This antibody response is not unexpected but may indicate an alternate vaccine-related immune mechanism or absence of causality with the vaccine.

Additional study is needed to confirm whether the rate of myocarditis-like illness is higher after vaccination than the background rate of myocarditis among similarly aged individuals in the population. Globally, myocarditis is diagnosed in approximately 10 to 20 individuals per 100 000 person-years.[5] Moreover, careful immunophenotyping studies are needed to investigate potential mechanisms of vaccine-associated myocardial injury. Such studies could help determine populations at higher risk of this potential outcome and possible treatment strategies and should inform clinicians of the possibility of a myocarditis-like illness in patients with appropriate symptoms in the first few days after COVID-19 vaccination. Treatment considerations for myocarditis include anti-inflammatory medications and the addition of guideline-directed medical therapy if left ventricular ejection fraction is reduced,[5] although no data specific to vaccine-associated myocarditis are available.

The clinical course of vaccine-associated myocarditis-like illness appears favorable, with resolution of symptoms in all patients. Given the potential morbidity of COVID-19 infection even in younger adults, the risk–benefit decision for vaccination remains highly favorable. Vaccine adverse event reporting remains of high importance and further studies are needed to elucidate the pathophysiological mechanism to potentially identify or prevent future occurrences.

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.

Affiliations

Division of Cardiology, Inova Heart and Vascular Institute, Fairfax, VA (C.M.R., L.G., B.N.T., M.A., H.B., S.C., A.A.D., S.S.D., A.E., G.M., A. Maghsoudi, I.M.S., M.C.F., M.W.S., S.S.S., C.M.O'C., C.R.d.F.). Fairfax Radiology Centers, VA (M.A.). Departments of Internal Medicine and Pathology, University of Texas Southwestern Medical Center, Dallas, TX (J.A.d.L., A.K., A. Muthukumar). Virginia Heart, Falls Church, VA (I.M.S., A. Maghsoudi). Division of Cardiology, Duke University, Durham, NC (C.M.O'C.).

Acknowledgments

The authors acknowledge the Dudley Family for their continued contributions and support of the Inova Dudley Family Center for Cardiovascular Innovation. The authors also acknowledge Kee Hyo Kang, Dr Lucy Nam, and Holly O'Donnell for their laboratory contributions and support of this project.

Sources of Funding

Dr Damluji receives research funding from the Pepper Scholars Program of the Johns Hopkins University Claude D. Pepper Older Americans Independence Center funded by the National Institute on Aging (P30-AG021334) and a Mentored Patient-Oriented Research Career Development Award from the National Heart, Lung, and Blood Institute (K23-HL153771-01). Dr deFilippi receives funding from the National Center for Advancing Translational Science of the National Institutes of Health (award UL1TR003015).

Disclosures

Dr Tehrani is a consultant for Medtronic, and is on the advisory board for Abbott Medical and Retriever Medical. Dr Atkins is on the advisory board for Arterys. Dr de Lemos has received grant support from Abbott Diagnostics and Roche Diagnostics and consulting income from Siemen's Health Care Diagnostics, Ortho Clinical Diagnostics, and Quidel, Inc. Dr Desai serves on the Advisory Board at Abbott Medical. Dr. Muthukumar has received grant support from Abbott and Roche Diagnostics. Dr deFilippi receives research funding to Inova from Abbott Diagnostics, Roche Diagnostics, Siemens Healthineers, and Ortho Diagnostics; and consults for FujiRebio, Roche Diagnostics, Siemens Healthineers, and Ortho Diagnostics. The other authors report no conflicts.

REFERENCES

1. Damluji AA, Christenson RH, deFilippi C. Clinical application of serologic testing for coronavirus disease 2019 in contemporary cardiovascular practice. *J Am Heart Assoc*. 2021;10:e019506. doi: 10.1161/JAHA.120.019506
2. Menni C, Klaser K, May A, Polidori L, Capdevila J, Louca P, Sudre CH, Nguyen LH, Drew DA, Merino J, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. *Lancet Infect Dis*. 2021;7:939–949.
3. Su JR, McNeil MM, Welsh KJ, Marquez PL, Ng C, Yan M, Cano MV. Myopericarditis after vaccination, Vaccine Adverse Event Reporting System (VAERS), 1990-2018. *Vaccine*. 2021;39:839–845. doi: 10.1016/j.vaccine.2020.12.046
4. Mandavilli A. C.D.C. is investigating a heart problem in a few young vaccine recipients. *The New York Times*. May 22, 2021. https://www.nytimes.com/2021/05/22/health/cdc-heart-teens-vaccination.html?smid=em-share. Accessed May 25, 2021.
5. Tschöpe C, Ammirati E, Bozkurt B, Caforio ALP, Cooper LT, Felix SB, Hare JM, Heidecker B, Heymans S, Hübner N, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. *Nat Rev Cardiol*. 2021;18:169–193. doi: 10.1038/s41569-020-00435-x

Table. Patient Characteristics and Outcomes

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age, y	28	39	39	24	19	20	23
Sex	M	M	M	M	M	M	M
Race/ethnicity	White	White	White	White	Hispanic	White	White
Vaccine type							
mRNA		Y (Pf, 2nd)	Y (Mod, 2nd)	Y (Pf, 1st)	Y (Pf, 2nd)	Y (Pf, 2nd)	Y (Pf, 2nd)
Adenovirus	Y (J&J)						
Days from administration to presentation	5	3	4	7	2	3	3
History of previous COVID-19 infection	Denied/remote negative PCR	Denied/ negative PCR	Denied/ negative PCR	Denied/ negative PCR	Denied/ negative PCR	Yes/ negative PCR	Denied/ negative PCR
Presenting symptoms	Chest pain at rest, nonpleuritic, non-exertional; no fevers, coughing, or shortness of breath	Sudden onset 7 out of 10 chest pain 2 days after vaccine, associated with shortness of breath; worse when lying flat and with inspiration	Fever, chills, shortness of breath, and chest heaviness/pain symptoms	Intermittent, positional chest pain with left arm numbness and tingling	Midsternal sharp chest pain, waxing/ and positional; relieved with leaning forward	Midsternal chest pain with deep inspiration.	Subjective fevers, diffuse myalgia, and headache starting day of vaccination; sudden onset of sharp chest pain the night before admission that persisted at 3 out of 10 intensity, worsened when lying flat
Vital signs at presentation							
Temperature, °C	37	36.6	36.9	36.9	36.5	37.9	37.1
Heart rate, bpm	70	93	79	69	77	112	96
Blood pressure, mm Hg	145/82	116/76	103/70	114/56	108/71	121/78	131/80
Respirations, per min	18	18	16	16	18	18	16
Chest x-ray findings	No acute pulmonary disease	No acute process	No detectable active cardiopulmonary disease	No acute abnormality	No acute disease	No evidence of acute cardiopulmonary disease	No acute abnormality
ECG findings							
ST changes	1-mm ST elevation in II, V5–V6	PR depression in II, aVF, V4–V6 T wave inversion V1	No acute ST segment changes	No acute ST segment changes	Nonspecific ST-T changes	1-mm ST elevation V2–V5	Diffuse ST elevations
Rhythm	Normal sinus rhythm	Normal sinus rhythm	Normal sinus rhythm	Normal sinus rhythm	Normal sinus rhythm	Sinus tachycardia	Sinus tachycardia
Echocardiogram	6 days postvaccine	3 days postvaccine	4 days postvaccine	7 days postvaccine	2 days postvaccine	5 days postvaccine	4 days postvaccine
Left ventricular ejection fraction	51%	35% to 40%	61%	53%	55%	50% to 55%	58%
Left ventricular end-diastolic internal dimension	4.8 cm	4.9 cm	4.4 cm	5.2 cm	4.7 cm	4.34 cm	5.0 cm
Intraventricular septal diastolic thickness (2D)	1.0 cm	1.1 cm	1.0 cm	1.0 cm	0.6 cm	1.1 cm	1.0 cm
Regional wall motion abnormalities	Mild global hypokinesis	Mild global left ventricular hypokinesis; mildly decreased right ventricular function	None	None	None	Mild hypokinesis in the mid- to distal anteroseptum and apex	None
Diastolic function	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Cardiac magnetic resonance imaging	37 days postvaccine	11 days postvaccine	5 days postvaccine	7 days postvaccine	3 days postvaccine	6 days postvaccine	3 days postvaccine
Left ventricular ejection fraction	50% (no regional wall motion abnormalities)	56% (no regional wall motion abnormalities)	52% (no regional wall motion abnormalities)	48% (no regional wall motion abnormalities)	50% (no regional wall motion abnormalities)	52% (subtle apical septal and apical lateral hypokinesis)	50% (no regional wall motion abnormalities)

(*Continued*)

Table. Continued

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
LGE	Patchy mild subepicardial LGE throughout the mid- to apical left ventricular walls; no pericardial thickening or enhancement	Subepicardial LGE along the anterior and lateral walls; no pericardial thickening or effusion	Multifocal subepicardial and midmyocardial LGE; prominence of the pericardium overlying the anterior wall with enhancement	Midmyocardial LGE in the septal and inferior walls; subepicardial LGE in the anterior, lateral, and inferior walls; no pericardial effusion	Multifocal patchy subepicardial and midmyocardial LGE within the lateral and inferolateral walls; no pericardial thickening or enhancement	Subepicardial LGE within the lateral, inferolateral, and anterolateral walls with global left ventricular apex; no pericardial thickening or effusion	Basal anteroseptal mid wall delayed enhancement; trace pericardial enhancement
T1 mapping	1046 ms	1000 ms					1125 ms
T2	No definitive edema	No definitive edema	Suboptimal T2 WI secondary to banding artifact and respiratory motion	Myocardial edema in the lateral and inferior walls	Myocardial edema in lateral wall at the level of the base	Subtle inferior wall myocardial edema	No definitive edema
White blood cell count	8.08	9.01	8.28	11.14	8.33	10.56	9.46
Cardiac troponin I ng/mL (<0.04 ng/mL)							
Presentation	3.55	4.24	3.41	0.37	4.49	0.48	
Peak	17.08	11.01	13.00	0.37	44.80	8.36	
Postdischarge	<0.01	<0.01	0.037	ND	0.19	ND	
cTnI, ng/L (<17 ng/L)							
Presentation							2601
Peak							7000
Postdischarge							6
B-type natriuretic peptide, pg/mL	ND	22	97	<10	57.2	29	68
Erythrocyte sedimentation rate peak, mm/h	8	8	23	4	ND	10	32
C-reactive protein peak, mg/dL	1.3	5.1	11.70	0.1	3.1	8.2	7.3
Antinuclear antibody screen	Negative	Negative	Negative	ND	Negative	ND	ND
SARS-CoV-2 antibody							
Spike IgG	Negative*‡	Positive*	Positive‡	Negative§	Positive*	ND	Positive†
Nucleocapsid IgG	Negative†	Negative†	ND	ND	Negative†	ND	Negative†
Respiratory viral panel‖	ND	ND	Negative except mycoplasma IgG; Coxsackie B1, B2, B3 (IgG 1:8) and B4, B5, B6 (IgG 1:16)	Negative	Negative	Negative	Negative except Coxsackie B4 (IgG 1:320)
Coronary angiography findings	No evidence of coronary artery disease	No evidence of coronary artery disease	No obstructive coronary artery disease; proximal circumflex; mild 30% stenosis	ND	ND	ND	ND
Clinical course							
Hospitalization duration	2 days	4 days	3 days	2 days	3 days	4 days	2 days
Treatment(s)	β-blocker, angiotensin-converting enzyme inhibitor, aspirin, and clopidogrel (2 doses, stopped on discharge)	β-blocker, angiotensin receptor blocker, statin	3 days IV steroids	Colchicine, ibuprofen, famotidine	Colchicine, ibuprofen, famotidine	Ibuprofen, famotidine	β-blocker, colchicine

T1 mapping refers to native T1 values obtained by the Modified Look-Locker Inversion recovery pulse sequence. T2 images were acquired by T2 mapping or short axis T2-weighted fat saturated sequence. 2D indicates two dimensional; COVID-19, coronavirus disease 2019; cTnI, high sensitivity cardiac troponin I; IgG, immunoglobulin G; IgM, immunoglobulin M; IV, intravenous; J&J, Johnson and Johnson (New Brunswick, NJ); LGE, late gadolinium enhancement; Mod, Moderna vaccine (mRNA-1273; Cambridge, MA); ND, testing not obtained; PCR, polymerase chain reaction; Pf, Pfizer-BioNTech COVID-19 vaccine (BNT162b2; Philadelphia, PA); and SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

*Performed using Siemens Healthineers Dimension EXL SARS-CoV-2 IgG assay.

†Performed using Abbott ARCHITECT SARS-CoV-2 IgG.

‡Performed using DiaSorin LIAISON SARS-CoV-2 S1/S2 IgG assay.

§Performed using Healgen COVID-19 IgG/IgM Rapid Test Cassette.

‖Respiratory viral panel was performed using the FilmArray BioFire Respiratory Panel 2.1 and contains qualitative detection of respiratory pathogen nucleic acid for the following viruses: adenovirus, coronavirus 229E, coronavirus HKU1, coronavirus NL63, coronavirus OC43, SARS-CoV-2, human metapneumovirus, human rhinovirus/enterovirus, influenza A, influenza A/H1, influenza AH1 2009, influenza A/H3, influenza B, parainfluenza virus 1, parainfluenza virus 2, parainfluenza virus 3, parainfluenza virus 4, respiratory syncytial virus, *Bordetella pertussis, Bordetella parapertussis*, *Chlamydophila pneumoniae*, and *Mycoplasma pneumoniae*.