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Myocarditis Temporally Associated with COVID-19 Vaccination

Running Title: *Rosner et al.: Myocarditis after COVID-19 Vaccination*

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Non-standard Abbreviations and Acronyms:
COVID-19 = Coronavirus disease-2019
ECG = Electrocardiogram
ACE-I= angiotensin converting enzyme-Inhibitor
ANA= antinuclear antibody
ARB= angiotensin receptor blocker
ASA= aspirin
BB= beta-blocker
BNP= brain natriuretic peptide
CAD= coronary artery disease
CRP= c-reactive protein
CTA= coronary computed tomography angiogram
cTnI= Cardiac Troponin I
ESR= erythrocyte sedimentation rate
HKN= hypokinesis
hs-cTnI = high sensitivity cardiac troponin I
IV= intravenous
IVS= intraventricular septal diastolic thickness (2D)
J&J= Johnson & Johnson (Janssen Biotech, Inc., a Janssen Pharmaceutical company, Johnson & Johnson; New Brunswick, New Jersey)
LV= left ventricle
LVEDP= left ventricular end-diastolic pressure
LVEF= left ventricular ejection fraction
LVIDd= left ventricular end-diastolic internal dimension
Mod= Moderna (mRNA-1273) vaccine (ModernaTX, Inc.; Cambridge, Massachusetts)
MRI = magnetic resonance imaging
NSR= normal sinus rhythm
Pf= Pfizer-BioNTech COVID-19 (BNT162b2) vaccine (Pfizer, Inc.; Philadelphia, Pennsylvania)
RAD= right axis deviation
RBB= right bundle branch block
RWMA= regional wall motion abnormalities
T1 mapping- Native T1 values obtained by the Modified Look-Locker Inversion recovery (MOLLI) pulse sequence
T2– Images acquired by T2 mapping or SA T2FS sequences
WBC= white blood cell count

The global coronavirus disease-2019 (COVID-19) pandemic brought significant mortality with over 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 FDA approval: Pfizer-BioNTech COVID-19 (BNT162b2, Pfizer, Inc; Philadelphia, Pennsylvania), Moderna (mRNA-1273, ModernaTX, Inc; Cambridge, Massachusetts) and Janssen (Ad.26.COV2.S) (Johnson & Johnson; New Brunswick, New Jersey) (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 US and 894 million individuals worldwide had received at least one 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 following COVID-19 vaccination, from 2 US medical centers in Falls Church, VA and Dallas, TX. All were males < 40 years of age and of White or Hispanic race/ethnicity (Table). Only 1 patient reported prior history of COVID-19 infection. Six patients received mRNA (Moderna or Pfizer/BioNTech) and 1 received the adenovirus (Johnson & Johnson) vaccine. All patients presented 3-7 days post vaccination with acute onset chest pain and biochemical evidence of myocardial injury, by cardiac troponin I (Abbott Diagnostics, Lake Forest, IL) (mean peak = 15.77ng/mL, median peak = 12.01ng/mL), or elevated high sensitivity troponin I (Abbott Diagnostics, Lake Forest, IL) (peak=7000ng/L). All were hemodynamically stable and none had a pericardial friction rub or rash. Electrocardiogram (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 (LVEF) ranging from 35% to 62% with 5/7 having some degree of hypokinesis. Patients underwent cardiac magnetic resonance (CMR) 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 (LGE). Multi-focal subepicardial LGE was present in 7/7 patients and additional mid-myocardial LGE was demonstrated in 4/7 patients. There was corresponding myocardial edema in 3/7 patients. Two patients who underwent CMR > 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. None reported palpitations and there was no evidence of sustained arrhythmias. None had evidence of an active viral illness or autoimmune disease and 6/7 had PCR testing for acute COVID-19 infection during hospitalization, which was negative. Assessment of COVID-19 serology was obtained for 6/7 patients, with 4/6 showing presence of spike protein IgG antibodies.

Treatment varied and included beta-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 (VAERS) and the CDC. Institutional review board approval was obtained for this report. The data that support the findings of this study are available from the corresponding author upon reasonable request.

In 1990, the US established VAERS and from 1990-2018, 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 CDC 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 CMR 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 if the rate of myocarditis-like illness is higher after vaccination than the background rate of myocarditis among similar aged individuals in the population. Globally, myocarditis is diagnosed in approximately 10-20 individuals per 100,000/year (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 to the possibility of a myocarditis-like illness in patients with appropriate symptoms in the first few days following COVID-19 vaccination. Treatment considerations for myocarditis include anti-inflammatory medications, and addition of guideline directed medical therapy if LVEF is reduced (5), though no data are available specific to vaccine-associated myocarditis

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.

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Dr. Tehrani is a consultant for Medtronic, and he 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

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Table. Patient Characteristics and Outcomes

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age	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 prior 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, non-pleuritic non-exertional No fevers, coughing or shortness of breath	Sudden onset 7/10 chest pain 2 days after vaccine, associated with shortness of breath; worse when lying flat and with inspiration	Fever, chills and shortness of breath, chest heaviness/pain symptoms	Intermittent, positional chest pain with L arm numbness and tingling	Mid-sternal sharp chest pain, waxing and waning and positional. Relieved with leaning forward.	Mid-sternal chest pain, with deep inspiration.	Subjective fevers, diffuse myalgia and headache starting day of vaccination. Sudden onset of sharp chest pain the night prior to admission that persisted at 3/10 intensity, worse 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 (mmHg)	145/82	116/76	103/70	114/56	108/71	121/78	131/80
Respirations (per min)	18	18	16	16	18	18	16
CXR 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
EKG findings							
ST changes	1mm ST elevation in II, V5-V6	PR depression	No acute ST segment changes	No acute ST segment changes	Nonspecific ST-T changes	1mm ST elevation V2-5	Diffuse ST elevations

		in II, AVF, V4-V6 T wave inversion V1					
Rhythm	NSR	NSR	NSR	NSR	NSR	Sinus Tachycardia	Sinus Tachycardia
Echocardiogram	*6 days post vaccine*	*3 days post vaccine*	*4 days post vaccine*	*7 days post vaccine*	*2 days post vaccine*	*5 days post vaccine*	*4 days post vaccine*
LVEF	51%	35-40%	61%	53%	55%	50-55%	58%
LVIDd	4.8cm	4.9cm	4.4cm	5.2cm	4.7cm	4.34cm	5.0cm
IVS	1.0cm	1.1cm	1.0cm	1.0cm	0.6cm	1.1cm	1.0cm
RWMA	Mild global HKN	Mild, global LV HKN Mildly decreased RV 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 MRI	*37 days post vaccine*	*11 days post vaccine*	*5 days post vaccine*	*7 days post vaccine*	*3 days post vaccine*	*6 days post vaccine*	*3 days post vaccine*
LVEF	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)
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 mid myocardial LGE. Prominence of the pericardium overlying the anterior wall with enhancement.	Mid myocardial LGE in the septal and inferior walls. Subepicardial LGE in the anterior, lateral and inferior walls. No pericardial effusion.	Multifocal patchy subepicardial and mid myocardial 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	1046ms	1000ms					1125ms
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

WBC	8.08	9.01	8.28	11.14	8.33	10.56	9.46
cTnI, 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	
Post Discharge	<0.01	<0.01	0.037	ND	0.19	ND	
hs-cTnI ng/L *(<17 ng/L)*							
Presentation							2601
Peak							7000
Post Discharge							6
BNP, pg/mL	ND	22	97	<10	57.2	29	68
ESR, peak, mm/hr	8	8	23	4	ND	10	32
CRP, peak, mg/dL	1.3	5.1	11.70	0.1	3.1	8.2	7.3
ANA, screen	Negative	Negative	Negative	ND	Negative	ND	ND
SARS-CoV-2 Ab							
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 and B3 IgG 1:8; B4, B5, B6 IgG 1:16	Negative	Negative	Negative	Negative except Coxsackie B Type 4 IgG 1:320
Coronary angiography findings	No evidence of CAD	No evidence of CAD	No obstructive CAD. 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)	BB, ACE-I, ASA, and clopidogrel (2 doses, stopped on D/C)	BB, ARB, statin	3 days IV steroids	Colchicine, ibuprofen, famotidine	Colchicine, ibuprofen, famotidine	Ibuprofen, famotidine	BB, colchicine

ND = Testing not obtained

* Performed using Siemens Healthineers EXL SARS-CoV-2 IgG

† 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 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, Mycoplasma pneumoniae