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Brief Communication

Myocarditis presentation following COVID-19 virus infection versus COVID-19 vaccination

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Abstract: Coronavirus disease 2019 (COVID-19) vaccine-induced cardiac injury has recently emerged as a major public health concern around the globe. There are reported cases of COVID-19 vaccine-induced myocarditis, but they are generally extremely rare and mild. In contrast, COVID-19 infection can cause acute cardiac injury with poor prognosis and high mortality rates. Herein, we describe the difference in patients' presentation by comparing two cases of myocarditis. One after contracting COVID-19 virus infection with a severe clinical course, and the other patient developed myocarditis post-COVID-19 vaccine.

Keywords: COVID, vaccine, myocarditis

Introduction

Myocarditis is inflammation of the cardiac muscle and remains an important clinical condition in which the body's immune system causes inflammation in response to infectious or non-infectious agents. The onset of myocarditis often follows a viral infection. Vaccine-associated myocarditis is increasing as a complication of the mRNA vaccines. COVID-19 infection and COVID-19 vaccine often present with a spectrum of symptoms ranging from asymptomatic patients to those with serious consequences, such as myocarditis. This study reviewed two cases and discussed the differences in presentation of myocarditis after developing COVID-19 infection and other after receiving COVID-19 vaccination.

Case presentation

Case 1

A 69-year-old male with a past medical history of mild hypertension presented to the office after developing acute shortness of breath a few days after receiving second dose of the mRNA-1273 SARS-CoV-2 (Moderna) vaccine. He is active and exercises daily. His presentation was gradual worsening dyspnea on exertion over a few days combined with orthopnea and paroxysmal nocturnal dyspnea (PND). On physical exam, lungs are clear to auscultation, no murmurs or rubs, with no lower extremity swelling. He was normotensive with blood pressure of 125/79, respiratory rate of 15, heart rate of 80, and oxygen saturation of 96% on room air. Electrocardiography (ECG) showed sinus rhythm with frequent premature complexes. His ProBNP was elevated at 1586. His echocardiogram revealed severely reduced left ventricle systolic function with an ejection fraction (LVEF) 20-25%, normal right ventricle, and unremarkable valvular structures. His workup included a CT angiogram of the chest with minimal CAD. A cardiac MRI (**Figure 1**) showed LVEF of 38% and myocardial edema involving the basal and mid inferoseptal, inferior and inferolateral walls in a pattern consistent with myocarditis. He was started on goal-directed medical therapy with sacubitril-valsartan, spironolactone, furosemide, and carvedilol. His symptoms resolved with medical therapy. He is currently pending a repeat echocardiogram to re-evaluate his left ventricular systolic function. At 5 weeks outpatient follow-up, he did well, able

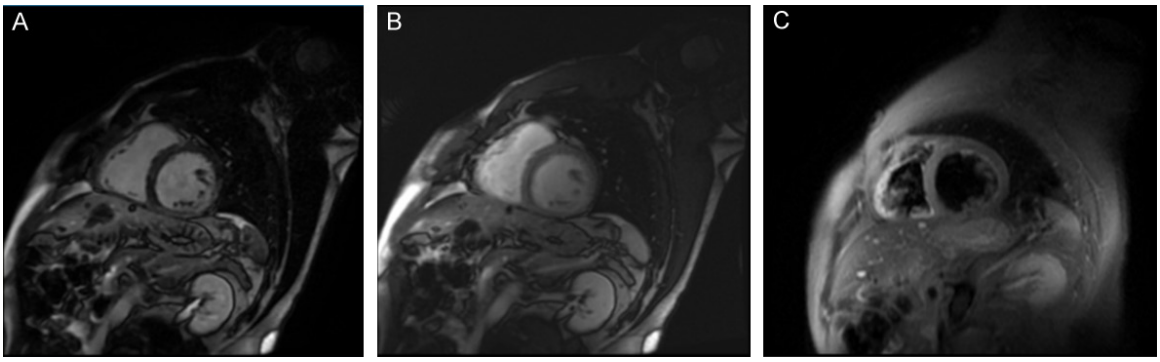

Figure 1. Acquisition protocol: MRI was performed on 1.5T MRI scanner (Optima MR450w, GE-Healthcare, Milwaukee, WI) using a dedicated cardiac phased array coil. Imaging sequences included black blood single-shot fast spin echo, bright blood balanced steady-state free precession gradient echo, T1 weighted inversion recovery early gadolinium enhanced (EGE) and late gadolinium enhanced (LGE) imaging. EGE and LGE were obtained 3 minutes and 7-10 minutes after single dose (0.1 mM/kg) of gadobenate dimeglumine (MultiHance, Bracco, Monroe Township, NY) intravenous contrast, respectively. A: LGE short axis image demonstrates mid LV anteroseptal, inferoseptal midwall and inferior, inferolateral wall subepicardial enhancement. B: EGE short axis image demonstrates mid LV anteroseptal, inferoseptal midwall and inferior, inferolateral wall subepicardial enhancement subepicardial enhancement suggesting hyperemia. C: T2-weighted black-blood short axis image demonstrates mid LV anteroseptal, inferoseptal, inferior and inferolateral wall edema.

to do daily activities without any discomfort. Repeat ECHO showed improvement in LVEF to 40%.

Case 2

A 46-year-old female with a past medical history of migraine presented to the emergency department (ED) with chest pain, shortness of breath, and fever. Tested positive for SARS-CoV-2 by RT-PCR (reverse transcription-polymerase chain reaction). On physical exam, lungs were clear to auscultation, with no murmurs or rubs and no lower extremity swelling. She was normotensive with blood pressure of 105/66, tachypneic with a respiratory rate of 21, tachycardic with a heart rate of 129, and oxygen saturation of 96% on room air. ECG showed sinus tachycardia. Her cardiac enzymes were elevated, Troponin T, 5th Gen 174 ng/l, CPK 195 EnzU/L, CK-MB 20.7 ng/mL, CK-Index 10.6, elevated pro-BNP 5037 pg/mL, elevated D-Dimer 1.66 ugFEU/mL, elevated C-Reactive protein 4.7 mg/dl and normal white blood cell count 6.6 × 10^3/mcL. ECHO showed LVEF of 25%, severe global hypokinesis. Cardiac catheterization revealed normal coronary arteries, low pulse pressure, reduced cardiac output with a cardiac index of 1.3 L/m^2, and elevated systemic vascular resistance at 1900 dynes-sec/cm^5. She was started on IV Milrinone, had an Impella LV support device placed, and was transferred to the cardiac intensive care unit for close monitoring. She received inotropic support for 4 days and, eventually, guideline-directed medical therapy for heart failure (losartan, metoprolol succinate, spironolactone) were started. She also received five days of IV dexamethasone 6 mg/day. Repeat Echocardiogram on day 5 showed recovered LVEF to 60%, thus Impella device was removed. She was discharged on hospital day 10. At a 3-week outpatient follow-up, she did well, able to do daily activities without any discomfort.

Discussion

Since its emergence at the start of the worldwide pandemic, COVID has been implicated as a triggering cause of myocarditis and, subsequently, an indirect cause of myocarditis via vaccination.

We aimed to discuss the differences in patients' presentation by reporting 2 potential myocarditis patients. One in a 69-year-old male patient who developed mild myocarditis symptoms following mRNA-1273 SARS-CoV-2 (Moderna) vaccine and was managed on an outpatient basis. And one case in a 46-year-old female who developed cardiogenic shock requiring aggressive support and a prolonged hospital stay.

Myocarditis is an inflammatory disease of the myocardium with focal or diffuse involvement.

Viral and post-viral myocarditis remain major causes of acute myocarditis [12]. Vaccine-associated myocardial injury is rare; however, it has been recorded in the case of influenza, COVID-19, and smallpox vaccines [1-3]. Vaccines trigger an immune response to form neutralizing antibodies that provide protection against infection. Although the exact cause and mechanism of the myocardial injury are not known, there are some suggestions that post-vaccine lymphocytic infiltration can result in immune-mediated cardiac injury.

The COVID-19 virus may cause cardiomyocyte damage due to abnormal immune responses caused by inappropriate activation of innate and adaptive immune systems [19, 20], as seen in other types of viral myocarditis. Literature has shown both COVID directly via natural infection and COVID antigen, derived via vaccination, can trigger cytokine storm in those with yet-identified predisposed risk [30]. Albeit with generally differing degrees of severity, with vaccination-mediated is generally milder versus the natural-infection-mediated myocarditis [28, 29].

Future clinical studies are required to clearly define the pathophysiological mechanisms triggering myocardial injury in COVID-19 patients. The CDC estimates that the incidence of myocarditis following any COVID-19 vaccine is 0.48 incidences per 100,000 using data from the Vaccine Adverse Event Reporting System.

Male patients have a higher prevalence of acute myocarditis [3, 14]. Male predominance is most likely due to sex hormone differences such as testosterone which inhibits anti-inflammatory cells [16, 17]. The Kyto et al. [15] study evaluated 3274 hospitalizations for myocarditis during 9.5-year period and reported that myocarditis is more common in males, although female patients often have a more severe manifestation. Children are more susceptible to fulminant myocarditis with severe manifestations as compared to adults [18].

According to CDC, patients who experience shortness of breath, chest pain, or palpitations within 7 days of receiving the COVID-19 vaccine should be evaluated for myocarditis. Clinical presentation of myocarditis is variable, with manifestations ranging from subclinical disease to sudden death [11]. The European Study of the Epidemiology and Treatment of Inflammatory Heart Disease [13] tested 3055 individuals with suspected myocarditis and found that 72% of them experienced dyspnea, 32% had chest discomfort, and 18% had arrhythmias. Shortness of breath, fatigue, chest pain, and lethargy are the most common presenting symptoms of COVID-19 infection-induced or post-vaccine-related myocarditis. Fulminant myocarditis, which is characterized by sudden and severe diffuse cardiac inflammation, typically develops within three weeks of contracting the virus and manifests as ventricular arrhythmia, cardiogenic shock, and acute onset of heart failure [9, 10].

There is no sensitive or specific non-invasive diagnostic test that can confirm the diagnosis of myocarditis. ECG of confirmed myocarditis patients may demonstrate ST-segment changes, including ST-segment elevation, frequent ectopy, ventricular arrhythmias, and conduction abnormalities with advanced atrioventricular nodal block [9]. A low QRS voltage [22] may be observed in fulminant myocarditis as a result of myocardial edema. According to the findings of the Ukena et al. [21], suspected myocarditis patients with prolonged QRS duration are a significant independent predictor of cardiac death or heart transplantation. ECG findings are not sensitive in detecting myocarditis, and their absence does not rule out the condition.

The guidelines proposed by the American Heart Association (AHA) recommend further testing for patients with suspected myocarditis with cardiac imaging such as ECHO and cardiovascular magnetic resonance (CMR) [10]. ECHO is the first line and most often used imaging modality for determining cardiac structure and function. Portability and real-time imaging are significant benefits for quickly evaluating the severity of cardiac dysfunction. The cardinal characteristics of myocarditis determined by an ECHO include left ventricular systolic dysfunction, diastolic dysfunction, right ventricular dysfunction, cardiac thrombus, increased wall thickness, chamber dilation, or hypokinesis [23, 24]. However, normal left ventricular systolic function does not exclude myocarditis. Patients with fulminant myocarditis may have increased septal thickness and frequently lack cardiac dilation with greater recovery, whereas

patients with acute myocarditis have increased diastolic dimensions but normal septal thickness [25].

Gadolinium contrast-enhanced cardiac magnetic resonance (CMR) provides unique insights into tissue-level pathologies consistent with myocarditis, such as myocardial edema, irreversible cell injury, hyperemia, and fibrosis, in addition to suggestive functional and morphological features (e.g., right ventricular and LV size and function, pericardial effusion) [26]. In contrast to conventional imaging, contrast CMR gives information on the precise location of cardiac damage produced by myocarditis that can be utilized to guide biopsy, hence improving sensitivity and specificity [27]. American Heart Association (AHA) and the European Society of Cardiology (ESC) recommend an endomyocardial biopsy (EMB) as the definitive diagnostic test for myocarditis, but it has low sensitivity.

Current medical treatment of COVID-19 infection/vaccine-related myocarditis focuses on corticosteroids and intravenous immunoglobulins (IVIG) to halt the progression of diffuse non-specific immune system activation [9, 33]. However, the efficacy and safety of corticosteroids in viral myocarditis remain controversial. In patients with left ventricular systolic dysfunction, guideline-directed therapy, including β-blockers and angiotensin-converting enzyme inhibitors, should be initiated. In patients with low cardiac output not responding to maximal pharmacological therapy, mechanical circulatory support (MCS) can be used.

Reports from Israel [3, 4] document that myocarditis following the COVID-19 vaccine is rare and mild. Multiple studies [5-8] have revealed a high incidence of COVID-19 infection-induced acute and chronic damage to the cardiovascular system associated with high mortality and morbidity. Cardiac dysfunction following COVID-19 infection likely has worse outcomes than cardiac dysfunction following COVID-19 vaccine. Based on the known potential risk of complications associated with COVID-19 infection, including hospitalization, myocarditis, multisystem inflammatory syndrome, [31] and post-acute sequelae of COVID infection [32] and mortality even in younger individuals, the risk-benefit decision for immunization remains largely in favor of vaccination.

Key limitation of our study is that it is a small study including two cases. Despite limitations, it is notable that the clinical course of the patient who developed myocarditis following COVID-19 vaccination was mild. According to current literature, the benefits of vaccination outweigh its potential risks. So widespread vaccination is recommended. Nevertheless, we recommend additional research to evaluate the adverse effects of the COVID-19 vaccine.

Conclusion

We report the case of a 69-year-old male patient who developed shortness of breath following the mRNA-1273 SARS-CoV-2 (Moderna) vaccine and was diagnosed with myocarditis on work up, which was mild and managed outpatient with recovery. Whereas another case of 46-year-old female developed cardiogenic shock, CHF requiring ICU stay following COVID-19 infection.

- COVID-19 vaccine and COVID-19 infection can both cause myocardial injury. We want to emphasize that the severity of myocardial injury is worse with COVID-19 infection and encourage patients to vaccinate against COVID-19.

- In the appropriate clinical situation, physicians should maintain suspicion for myocarditis following the COVID-19 vaccine.

- Advantages of vaccination outweigh the risk, given that cardiac dysfunction following COVID-19 infection has higher morbidity and mortality, whereas myocarditis following COVID-19 vaccine is mild and uncommon, and most patients recover.

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Disclosure of conflict of interest

None.

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