Severe myopericarditis following the third dose of an mRNA COVID-19 vaccine: utility of a multimodal treatment approach

Rachel Olivia Fritz, Omkar Betageri, Teja Chakrala, Justin Kim, Mohammad Al-Ani, Abdullah Omar

SUMMARY
We report a rare case of severe myopericarditis in a healthy man in his 20s after the third dose of an mRNA COVID-19 vaccine. His symptoms and troponinemia resolved with a beta-blocker in addition to standard anti-inflammatory therapy, highlighting the utility of multimodal therapy.

BACKGROUND
Myopericarditis as an adverse event after mRNA COVID-19 vaccination (including Pfizer-BioNTech and Moderna) is a rare phenomenon with an overall incidence of 0.3–5.0 cases per 100,000 vaccinated people. It is a diagnosis of exclusion, made after ruling out common aetologies such as viral illness. Although observed in all demographics, it is most common in men 12–29 years old, after the second vaccine dose, and within a week of vaccination. Myopericarditis can also occur due to the COVID-19 virus, though affected patients are typically older and many have underlying cardiac disease or other medical comorbidities. While viral-induced myopericarditis is often severe, most vaccine-induced cases typically resolve spontaneously or with non-steroidal anti-inflammatory drugs and colchicine with a minority requiring hospitalisation and prolonged treatment regimens. In clinical practice, acute myocarditis and pericarditis can be difficult to distinguish and often occur as a spectrum of disease involving both the myocardium and pericardium to varying degrees.

Most studies to-date have examined cases of myopericarditis after the first or second mRNA vaccine dose, although a study from National Health Service data showed an elevated risk after the third dose of the Pfizer vaccine, specifically for men less than 40 years of age. This risk was only slightly higher than the risk after the second dose (13 vs 12 events per million, respectively). Our case report provides the first in-depth look at a case of severe myopericarditis following the third dose of an mRNA COVID-19 vaccine.

CASE PRESENTATION
A previously healthy man in his 20s presented with a chief complaint of aching, non-exertional, positional, and pleuritic substernal chest pain. Three days prior, he received the third dose of the Pfizer-BioNTech COVID-19 vaccine. The day following vaccination, he experienced subjective fever, chills, headache, myalgias and generalised malaise, which were alleviated with ibuprofen. On the morning of presentation, he developed the stated chest pain, which prompted him to seek medical attention.

On presentation, his vitals were significant for a temperature of 101.2°F and a heart rate of 95 beats per minute. Physical examination was significant for a pericardial friction rub. Laboratories were significant for a C-reactive protein of 31.02 mg/L (reference <20 pg/mL) (figure 1). All other laboratory findings, including D-dimer, were within normal limits. Respiratory PCR panel was negative for coronavirus 2 infection as well as 23 other viral and bacterial pathogens listed in the online supplemental figure 1.

INVESTIGATIONS
ECG (figure 2) showed mild ST segment elevation in V3–V6 as well as Spodick’s sign, a down-sloping TP segment seen as an early ECG manifestation in patients with acute pericarditis. A delta wave was incidentally noted without any clinical symptoms or arrhythmias.

Transthoracic echocardiography (TTE) revealed a borderline-depressed left ventricular ejection fraction, which was later characterised by cardiac MRI (cMR) as 62%. Trace pericardial effusion and hypokinesis of the mid-anteposterior wall segments were noted on TTE, but absent on cMR.

cMR additionally revealed late gadolinium enhancement (LGE) involving the subepicardial inferior, inferolateral and apical septal walls, with associated elevations of T1 and T2 times in those regions (figure 3). These cMR findings satisfied the modified Lake Louise criteria (LLC), the current cMR criteria used for patients with suspected myocarditis (figure 4).

DIFFERENTIAL DIAGNOSIS
Our differential diagnosis included myocarditis, acute coronary syndrome and other coronary syndromes such as coronary artery dissection or coronary vasospasm. We decided against performing coronary angiography to rule out coronary syndromes given the clear cMR evidence supporting myocarditis.
TREATMENT
His troponins continued to trend up, peaking at 3290 pg/mL (figure 1). The patient was started on high-dose aspirin, colchicine and indomethacin. Despite initial treatment, he was symptomatic of his presenting chest pain, concomitant with increasing troponins. He had a short run of non-sustained ventricular tachycardia (NSVT) on the fourth hospital day for which metoprolol succinate 25 mg was started. The patient’s troponins began to trend down significantly after the addition of metoprolol (figure 1). He was ultimately discharged on metoprolol, colchicine and a slow taper of aspirin and indomethacin, as well as close outpatient follow-up.

OUTCOME AND FOLLOW-UP
At 1- and 3-month follow-up, the patient had no recurrence of symptoms. TTE at 1 month showed resolution of the regional wall motion abnormalities and pericardial effusion.

DISCUSSION
Diagnosis of patients with clinically suspected myopericarditis should begin with suggestive history and physical examination findings, as well as laboratory findings of elevated troponin, ECG abnormalities and inflammatory markers. Echocardiography is performed in all patients to evaluate ventricular function and other possibilities of cardiac dysfunction. Acute pericarditis is diagnosed if two of the following four criteria are met: chest pain, pericardial friction rub, characteristic ECG findings (new, diffuse ST segment elevation or PR depression) and pericardial effusion. Patients with additionally suspected myocarditis may undergo cMR to further characterise the extent of myocardial involvement and determine if they meet the updated LLC.

Compared with the original LLC, the updated 2018 LLC increased the sensitivity of this testing modality significantly in diagnosing myocarditis. The 2018 LLC require the presence of two T1- and T2-based imaging criteria rather than three criteria as present in the original LLC (figure 4) and have led to an improvement in sensitivity from 72.5% to 87.5%. T1 criterion is considered positive if increase of native T1 relaxation times or positive LGE is present. T2 criterion is positive if increase in T2 relaxation times or regional high T2 signal intensities on T2-weighted images, or an overall increased global T2 SI ratio is present on imaging.

Our patient exhibited LGE in several regions: the subepicardial basal to apical inferior and inferolateral walls and demonstrated elevated T1 and T2 time in these regions, thereby satisfying the updated 2018 LLC for acute myocarditis.

Our case demonstrates particularly extensive myocardial involvement and injury driven by COVID-19 vaccine-induced myopericarditis. In a large Israeli study of COVID-19 vaccine-induced...
myocarditis, the median peak troponin was 49 times the upper limit of normal (ULN). In comparison, our patient’s peak troponin was 165 times the ULN. Our patient also experienced a short run of NSVT, observed in only 5% of patients.7

After an initial troponin I of 1939 pg/mL, the patient’s troponins continued to increase, peaking at 3290 pg/mL on hospital day 2. Indomethacin was also started that day, with the following four troponins not showing a marked decrease (1427–2239 pg/mL). After initiation of metoprolol on hospital day 4, his troponins decreased to 420 pg/mL and continued to trend steadily downward, with a final measurement of 119 pg/mL (Figure 1). Additionally, his symptoms resolved, and he had no additional runs of ventricular tachycardia after addition of beta-blockade.

Based on Figure 1, a continued decrease in troponins was sustained after the initiation of metoprolol, leading to the suggestion that beta-blockade in addition to ongoing anti-inflammatory therapy may have augmented the decrease in troponin values. There may be a cumulative therapeutic effect of anti-inflammation combined with beta-blockade, which is independently associated with a decrease in myocardial work. Therefore, in subsequent cases of myopericarditis, it may be prudent to start a beta-blocker concurrently with an anti-inflammatory regimen to promote early myocardial recovery.

In other words, although beta-blockers are not currently part of the guideline-directed management for myopericarditis without concomitant heart failure or arrhythmia, they may be beneficial based on the robust biochemical (decrease in troponins) and clinical (improvement in symptoms) response seen in our patient. Dedicated study on beta-blockade therapy in the management of myopericarditis is necessary to characterise its clinical impact on a broader scale.

As more individuals receive mRNA-based COVID-19 boosters, clinicians should remain vigilant for new cases of myopericarditis, but should not discourage vaccination. It is important to consider that myopericarditis also occurs as a severe complication of COVID-19 virus, which can be prevented or mitigated with vaccination.3 After reviewing data on postvaccination myopericarditis, the Advisory Committee on Immunization Practices determined that the benefits of vaccination with mRNA COVID-19 vaccines clearly outweigh the risks for all recommended age groups.2

Contributors ROF was the lead author for this manuscript. She was the senior medical student caring for the patient, and she led the writing and revising of the manuscript. GB was the senior resident during the case. He was actively involved in the patient’s care, and he contributed to conceptualising, drafting and revising the manuscript. TC was a resident who contributed to patient care, drafting the manuscript (specifically parts of the Discussion section) and creating the cMR figure. JK was a resident who was actively involved in caring for the patient, revising the manuscript, creating the troponin versus time graft and adjusting the image quality of all figures. Mohammad Al-Ati was an attending physician who read the cMR and identified key images to use for our figures. He also helped conceptualise and revise the manuscript. Abdullah Omar was the attending physician during the case. He was directly involved in the patient’s care as well as conceptualising, writing and revising the manuscript.

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ORCID iD Omkar Betageri http://orcid.org/0000-0001-6568-0105

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