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

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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.[1] It is a diagnosis of exclusion, made after ruling out common aetiologies 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.[2] 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.[3] 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).[4] 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 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 C reactive protein of 31.02 mg/L (reference range 0.0–5.0 mg/L) and high-sensitivity troponin I of 1219 pg/mL (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-anterolateral wall segmented 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 myopericarditis, 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.
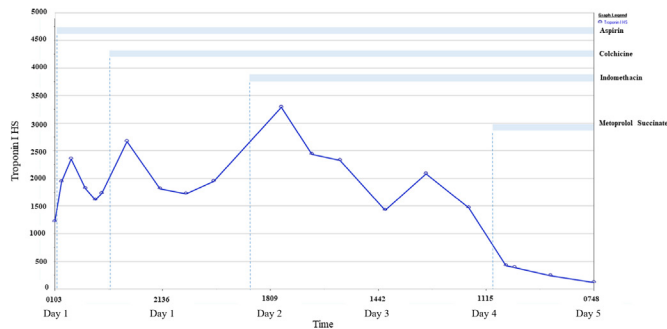
Figure 1 Troponin levels over time. Graph illustrating troponin levels as a function of time and addition of various medical therapies. Troponin I HS, high-sensitivity troponin I.

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
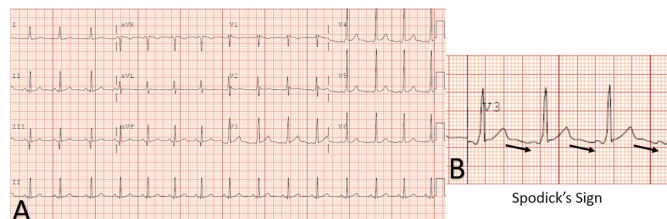

Figure 2 ECG on admission. (A) Standard 12-lead ECG showing normal sinus rhythm, mild ST elevation in leads V3–V5 and a delta wave indicating ventricular pre-excitation. (B) Arrows emphasise Spodick's sign, a down-sloping TP segment sometimes seen in early acute pericarditis.
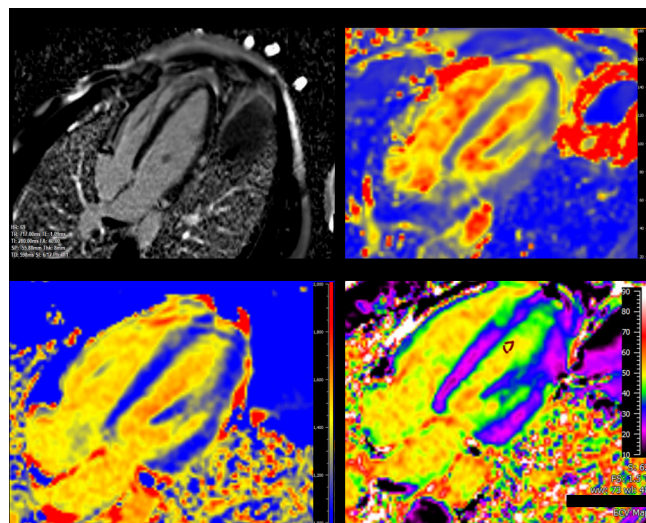

Figure 3 Cardiac magnetic resonance imaging. (A) Four-chamber phase-sensitive inversion recovery image. Ten-minute post-gadolinium showing uptake in the lateral and septal walls. (B) Four-chamber T1 map (ShMOLLI) showing increased T1 time in the mid-lateral and septal walls, corresponding to areas of late gadolinium enhancement (LGE) (normal <1050 ms). (C) Four-chamber T2 map showing oedema in the mid-lateral and septal walls, corresponding to areas of LGE and elevated T1 time (normal <55 ms). (D) Extracellular volume (ECV) mapping showing increased ECV in the affected areas (normal <28%).

diagnosing myocarditis.[5] 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%.[5 6] T1 criterion is considered positive if increase of native T1 relaxation times, increase of extracellular volume 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.[5 6] 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

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Updated Lake Louise Criteria – 2 out of 2 required

I. T1 – based findings:
    a. Regional (defined as an area of at least 10 contiguous pixels) or global increase in native myocardial T1 relation time or ECV; **or**
    b. Areas with high signal intensity in a non-ischemic distribution patter in LGE images

II. T2-based findings:
    a. Regional high T2 signal intensity; **or**
    b. Global T2 SI ratio ≥ 2.0 in T2W CMR images; **or**
    c. Regional or global increase of myocardial T2 relaxion time

Original Lake Louise Criteria – 2 out of 3 required

I. T2W imaging with regional high T2 SI or global T2 SI ratio ≥ 2.0 in T2W CMR images

II. Early gadolinium enhancement (EGE): SI ratio of myocardium/skeletal muscle (EGE ratio) of ≥ 4.0 in EGE images

III. Late gadolinium enhancement (LGE): Areas with high SI in a nonischemic distribution pattern in LGE images

Figure 4 Updated and original Lake Louise Criteria. ECV, extracellular volume; SI, signal intensity; T2W CMR, T2 weighted cardiac MRI.

myocarditis, the median peak troponin was 49 times the upper limit of normal (ULN).[7] 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 arrythmia, 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 Immunizations Practices determined that the benefits of vaccination with mRNA COVID-19 vaccines clearly outweigh the risks for all recommended age groups.[2]

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Patient's perspective

Three days after receiving my third dose of the Pfizer mRNA COVID-19 vaccine, I experienced chest tightness and shortness of breath, which later developed into persistent chest pain. Initially, I was going to brush it off as a minor vaccine side effect, but my girlfriend made me get into the car and go to the emergency room. Shortly after being treated at the emergency room, I was transported to the UF Vascular Hospital. There, I was given an initial diagnosis of myocarditis, which was later determined to be severe myopericarditis.

During the first 12 hours, I was in absolute shock. I had never in my life experienced a serious threat to my health, much less a cardiac event. And yet, my fear and anxiety quickly dissipated after meeting the UF cardiology team, who would treat me for 5 days until my release. The cardiologists, residents, medical students and nurses who took care of me there were peerless.

Since my discharge, I have not yet returned to normal life premyopericarditis. I am currently undergoing continued care to investigate the arrythmia detected while I was in the hospital. This has required me to stop weightlifting and make other lifestyle changes, but hopefully on a temporary basis. All in all, I consider myself lucky to be where I am now.

Lastly, I am especially grateful to the UF medical staff who cared for me during my treatment.

Learning points

► To highlight a severe presentation of COVID-19 vaccine-induced myopericarditis.
► To demonstrate a diagnosis of myocarditis supported by updated Lake Louis Criteria.
► To recognise the utility of early use of beta-blockade therapy for myopericarditis with extensive myocardial involvement.

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