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Case report

Myopericarditis with hemorrhagic pericardial effusion following BNT162b2 mRNA COVID-19 vaccine☆

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ABSTRACT

Since the onset of the COVID-19 pandemic, to date, around 385 million cases have been diagnosed worldwide leading to an estimated 5.7 million death toll. Mass vaccination campaigns have been conducted to control the spread of infection with the most commonly used vaccines being Pfizer-BioNTech and Moderna. However, the adverse effects of vaccination have not yet been fully investigated. Of concern are some serious cardiovascular events such as myocarditis, pericarditis, or perimyocarditis development post-vaccination. Hemorrhagic pericardial effusion has not been reported. However, we report a case of myopericarditis with a hemorrhagic pericardial effusion that developed two weeks following BNT162b2 mRNA COVID-19 vaccination. We performed a complete workup identifying the underlying cause that did not yield any significant findings. Our patient was treated with colchicine and ibuprofen, and he made a full recovery. A follow-up cardiovascular magnetic resonance imaging (CMR) showed no signs of active inflammation.

Introduction

According to the World Health Organization (WHO), the Coronavirus-19 (COVID-19) pandemic has led to around 5.7 million deaths and affected many, prompting the need for vaccine development to lessen COVID-19 related complications and mortality. As of February 2, 2022, a total of 4.82 billion people received at least one dose of vaccine [1]. Myocarditis/perimyocarditis is a rare but serious adverse condition that can be reported post-vaccination. The reason for this development is unknown; however, it can possibly be attributed to greater systemic and immunologic reactogenicity of mRNA vaccines as compared with other vaccines [2]. On June 24, 2021, the Centers for Disease Control and Prevention (CDC) declared myocarditis and pericarditis as side effects of the COVID-19 vaccines. On June 23, 2021, the Advisory Committee on Immunization Practices concluded that the benefits of COVID-19 vaccination to individual persons and at the population level clearly outweighed the risk of developing myocarditis after vaccination. Hemorrhagic pericardial effusion (PE) has not been reported after administering mRNA vaccines. To the best of our knowledge, this is the first case report on hemorrhagic pericardial effusion following BNT162b2 mRNA COVID-19 vaccination.

Case presentation

A 74-year-old male with a history alcoholic cirrhosis and hypertension was presented to a local emergency department with fever, intermittent chills, and chest and back pain. The pain was worse when lying flat and relieved by leaning forward. The patient reported that the symptoms began showing around 5 weeks prior, two weeks after he received his second dose of COVID-19 vaccine (Pfizer). He was given five doses of prednisone, but he did not show any improvements. The patient had no known COVID-19 exposures, history of recent viral illness, or other known risk factors.

On examination, his temperature was 36.1 °C, blood pressure was 110/62 mm Hg, heart rate was 87 beats/min, respiratory rate was 16 breaths/min, and the O_2 saturation was 90% on ambient air. His general cardiovascular and respiratory examination results were normal.

An initial laboratory workup showed mild leukocytosis with a white blood cell (WBC) count of 15,000 cells/mm^3, and elevated inflammatory markers of C reactive protein (CRP) of 247 mg/L (normal < 5 mg/L).

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Serial cardiac enzymes were normal. The nasopharyngeal swab test for SARS-CoV-2 (reverse transcription polymerase chain reaction) gave a negative result.

The patient's ECG showed new-onset atrial fibrillation and his chest X-ray (CXR) confirmed clear lungs with no abnormality. CT chest with IV contrast was ordered to rule out pulmonary embolism, and it revealed new pericardial effusion. Transthoracic echocardiography showed a large circumferential pericardial effusion without tamponade physiology (Fig. 1). Pericardiocentesis and drainage were performed, draining 560 mL of bloody effusion in total. The pericardial fluid was subsequently sent for culture, cell analysis, and cytology.

Pericardial fluid analysis revealed 201,000 red blood cells per mm^3, 2375 cells per mm^3 with 67% lymphocytes, negative Gram stain, and acid-fast bacilli (AFB) stain. Both bacterial and fungal cultures remained negative. A16S rRNA gene amplification and sequencing test revealed negative results. Cytological examination did not show malignant cells. An intensive work-up was performed for identifying a cause. A computed tomography scan of chest, abdomen, and pelvis ruled out tumor masses. Autoimmunity study, QuantiFERON, antineutrophil cytoplasmic antibody (ANCA), serum angiotensin converting-enzyme (ACE) and Lyme serology all showed negative results. Antibody test for coxsackievirus, cytomegalovirus (CMV), Epstein-Barr virus (EBV), parvovirus B19, human herpesvirus 6 (HHV6), human immunodeficiency virus (HIV), and hepatitis C virus (HCV) were negative.

The patient had an immediate symptomatic relief following the drainage of the pericardial fluid. His blood cultures were negative at 48 h, so he was discharged and scheduled for a close follow-up.

The patient was doing well for a week after discharge from the hospital until he started to have back pain, intermittent fever, and chills again. He was admitted again to the hospital, and repeated thoracic echocardiogram showed a small precordial effusion. Therefore, treatment with ibuprofen 600 mg three times a day and colchicine 0.5 mg twice a day was initiated. Cardiovascular magnetic resonance imaging (CMR) was done to exclude possible infiltrative etiology of myopericarditis. The imaging revealed no signs of active inflammation (Fig. 2), but it did show a small area of epicardial enhancement characteristic of prior myocarditis (Fig. 3).

On a four-week follow-up, the patient reported a complete relief of chest pain. Both colchicine and ibuprofen were thus discontinued.

Discussion

Acute pericarditis occurs when the bi-layered pericardial sac becomes inflamed. In most cases, the cause of pericarditis is idiopathic or assumed to be due to a viral infection [3]. While pericardial effusions might develop as a result of pericarditis, they are usually minor and rarely lead to cardiac tamponade. Acute myocarditis can result from a focal or diffuse infection of the myocardium [4]. Myopericarditis occurs when the inflammation extends to the pericardium, and it can be very difficult to distinguish it from pure myocarditis or pericarditis using routine emergency department tests. As is the case with pericarditis, viruses are the most common causative agents in myocarditis, but the cause can also be bacterial, fungal, or noninfectious. Elevated levels of troponin I are reasonably characteristic of pericarditis and myocarditis. They are not, however, specific to either syndrome [3,4].

Myocarditis and pericarditis are relatively rare diseases. The

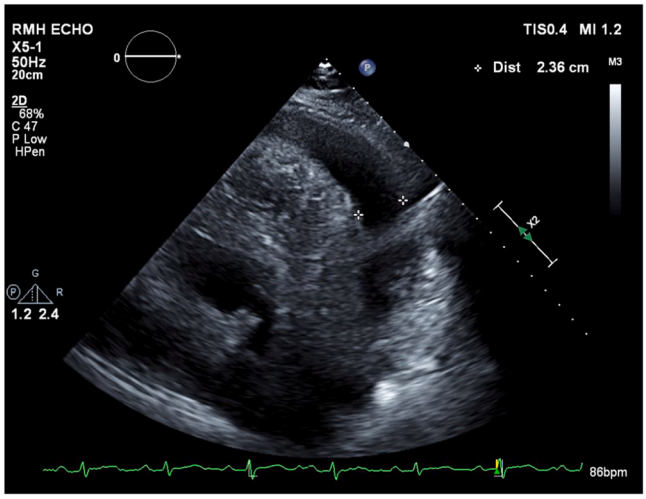

Fig. 1. Transesophageal echocardiogram (TTE): large circumferential pericardial effusion without tamponade physiology. Posteriorly, the effusion measure was 2.43 cm, and anteriorly, it was 1.43 cm.

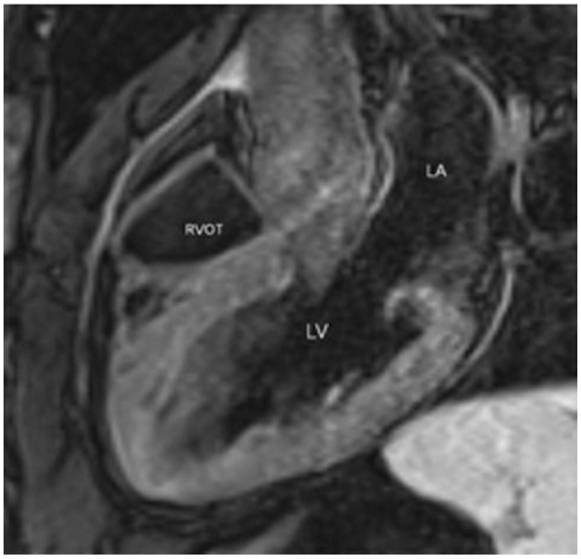

Fig. 2. Three-chamber T2-weighted image of left ventricle (LV) and right ventricular outflow tract (RVOT) with T2-weighted TSE sequences: There was no significantly increased signal intensity in the T2-weighted images to suggest edema of active inflammation. The T2-weighted images made before contrast showed mildly increased signal in the septal and lateral free wall of the LV on 3-chamber view and in the mid to anteroapical LV wall in the 2-chamber view.

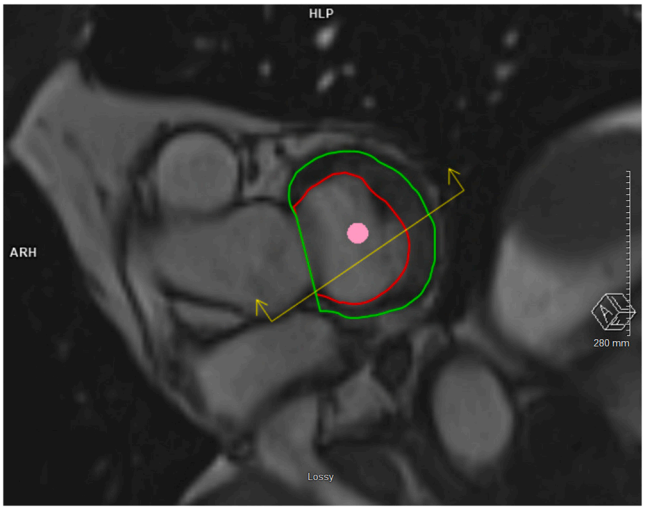

Fig. 3. Three-chamber (L) and basal short-axis slice (R) of small area of epicardial DE (arrows): A small area of epicardial delayed enhancement (DE) was seen on the 3-chamber view and a corresponding short-axis slice in the MAG and PSIR sequences, characteristic of myocarditis (marked by arrows in images). The remainder of the RV and LV myocardium appeared free of DE.

incidence of acute myopericarditis is unknown; however, a global estimate of myocarditis' incidence is 10 cases per 100,000 person in a year [5]. Myocarditis following vaccination has been a very uncommon adverse effect [6], except for the smallpox vaccine that led to a reported incidence of 1:10,000 [7]. No patients developed myocarditis in the 416, 629 adults who received live measles, mumps, rubella, oral polio, yellow fever, and varicella vaccinations as per the Vaccine Safety Datalink [8]. Tawfik et al. described the only known case of hemorrhagic pericardial effusion following vaccination (13-valent pneumococcal conjugate vaccine), but no such cases have been reported since then [9].

Interestingly, SARS-CoV-2 infection has been identified as a cause of myocarditis in many patients [10–13]. The mechanism of injury remains unknown; however, current theories suspect that it could be due to direct infection, an immune-mediated response, or a combination of direct and indirect effects [14]. Most commonly, myocarditis results from viral infections, and less often, it stems from other pathogens, toxic or hypersensitivity drug reactions, sarcoidosis or giant-cell myocarditis [4]. A few cases have reported pericarditis following vaccination but in a very limited number of cases – one reported after administering 13-valent pneumococcal conjugate vaccine and a few following influenza vaccination [9,15], but it is hard to exclude a possibility that those cases occurred due to chance.

As of February 3, 2022, 250 million people or 75.4% of the population in the US have received at least one dose of COVID-19 vaccine. Since April 2021, there has been an increase in the number of myocarditis and pericarditis cases reported in the US after mRNA COVID-19 vaccination (Pfizer-BioNTech and Moderna) [1]. As of June 23, 2021, 716 cases of myocarditis or pericarditis following vaccination among people below 30 years of age have been reported. Of those 484 patients, 67% (323 cases) has been fully investigated by the CDC. From these 323 investigated cases, 96% (309 patients) cases were hospitalized, 295 were discharged from the hospital, and 79% had a full recovery of symptoms. Nine patients were still hospitalized at the time. Onset was usually within several days after vaccination, and a higher number of cases was reported after the second dose than the first dose. Notably, confirmed cases have occurred mostly in male adolescents and young adults aged 16 years or older [1]. None of these cases were however associated with hemorrhagic pericardial effusion.

A recent retrospective analysis of 2,000,287 individuals who received COVID-19 vaccination from Washington, Oregon, Montana, Los Angeles County, and California confirmed the reports about the incidence of myocarditis and pericarditis following COVID-19 vaccination in 47 patients [16]. Thirty-two patients were admitted to the hospital, although none to intensive care. The median for stay duration was 1 and 2 days for pericarditis and myocarditis respectively. There were no readmissions or deaths. At the last available follow-up, 36 patients experienced symptoms' resolution, and 14 patients showed improvement.

In addition, two recent reports in *JAMA Cardiology* report 30 patients with myocarditis, or inflamed heart muscles, less than a week after receiving either a Pfizer/BioNTech or Moderna mRNA COVID-19 vaccine [12,17]. While these events may indicate a higher prevalence of myocarditis than expected, both reports note their rarity. All of the patients recovered or were recovering at the time of these reports, without developing complications.

The authors of the larger report, which described myocarditis in 23 US military men, noted that in the same period, the US Military Health System vaccinated more than 2.8 million people with mRNA-based COVID-19 vaccines. Hemorrhagic pericardial effusion was not described in these cases [17].

For the second study, the four cases of myocarditis identified at Duke University Medical Center were among more than 560,000 people estimated to have received two doses of an mRNA vaccine in the six surrounding counties. Again, there was no case of hemorrhagic pericardial effusion associated with myocarditis [12].

Pericarditis can occur in a variety of different infectious and non-infectious settings [18]. Hemorrhagic pericardial effusion has been described in patient with COVID-19 infection [19], but there have been no reports yet suggesting that it occurred after administering the COVID-19 vaccine. In addition, hemorrhagic effusion has been most commonly seen in patients with underlying malignancy or tuberculosis; however, it can also be observed in cases of uremic pericarditis, bacterial pericarditis, and pericarditis after myocardial infraction or following chest trauma or aortic dissection [20].

Our patient underwent extensive diagnostic investigation that excluded all of the potential, known causes of myopericarditis; therefore, COVID-19 vaccination seemed the most probable etiology. The disease course of our patient was mild. However, the clinical presentation can be more severe, including cardiogenic shock, ventricular arrhythmias, and progression to dilated cardiomyopathy [21]. Considering this, clinicians should maintain a high level of vigilance on all patients following vaccination. Recognition of COVID-19 vaccine–associated myopericarditis is important as the diagnosis would influence management and recommendations for exercise [22].

In the context of the current COVID-19 pandemic, it is of utmost importance to consider the rare adverse effects of COVID-19 vaccine, in view of the known serious complications following COVID-19 infection. COVID-19 has been associated with several cardiovascular complications, including myocardial injury and myocarditis, acute myocardial infarction (AMI), heart failure, dysrhythmias, and venous thromboembolism (VTE) [23]. It has been estimated that 8% of patients with COVID-19 have associated cardiac injury [24]. Early reports from China indicate that patients with myocardial involvement showed the worst outcomes. In-hospital mortality of patients with elevated troponin was as high as 60% [25]. Barda et al. published the largest real-world study of a COVID-19 vaccine to date that shows that Pfizer/BioNTech's shot is safe and linked to substantially fewer adverse events than SARS-CoV-2 infection in unvaccinated patients. They found that the risk of myocarditis increased by a factor of three after vaccination, which translated to approximately 3 additional events per 100,000 persons [26]. The importance of continued vaccination against COVID-19 cannot be underestimated. Given the remarkable effectiveness of COVID-19 vaccines at preventing symptomatic and asymptomatic SARS-CoV-2 infections and COVID-19–related hospitalizations, severe disease, and death, concerns about possible rare adverse events should not diminish the overall confidence in the effectiveness of vaccination.

Conclusion

Rare cases of cardiac inflammation following SARS-CoV-2 vaccination have been reported. Hemorrhagic pericardial effusion has however not been described before. Temporal association does not prove causation, although the short span between vaccination and myocarditis onset and the elevated incidence of myocarditis and pericarditis in the study hospitals lend support to a possible relationship. The risk of myopericarditis after receiving mRNA vaccine is far less than the risk of myopericarditis following COVID-19 infection. Therefore, there is no need to raise in undue alarm considering that one has to be vigilant about possible cardiac inflammation in vaccinated adults. The vaccination drive should continue uninterrupted, and there should be watchful awareness on part of clinicians and patients for alarming symptoms of cardiac inflammation.

CRediT authorship contribution statement

Gabriela S. Generette, James Troyer, Moamen Al Zoubi, Alice Hemenway: Writing – review & editing.

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Ethical approval

Written approval from ethics committee was obtained for publication of this case report and accompanying images. A copy of the written approval is available for review by the Editor-in-Chief of this journal on request.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Patient Consent Statement

The patient granted permission for this case to be published. The design of the current work has been approved by the Mercyhealth Offices of Research Administration and Privacy.

Conflicts of interest

Gabriela S. Generette – none; James Troyer – none; Moamen Al Zoubi – none; Alice Hemenway – none.

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