Coronavirus disease 2019 vaccination-related pericarditis: a single tertiary-center experience
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\textbf{Aims} Vaccination represents a cornerstone of prevention in the COVID-19 pandemic. Rare adverse events including acute pericarditis and myopericarditis have been reported.

\textbf{Methods} All consecutive patients referred to our referral center for pericardial diseases following COVID-19 vaccination from 1 April 2021 to 15 April 2022 were included. Acute pericarditis and myopericarditis were diagnosed according to ESC guidelines. Patients with SARS-CoV-2 infection were excluded from the study.

\textbf{Results} Twenty-four patients (79\% men) aged $39.7 \pm 19.8$ years were referred to our center with pericarditis after receiving COVID-19 vaccination. Thirteen (54\%) patients were diagnosed with myopericarditis. The mean time between vaccination and symptoms onset was $7.0 \pm 4.9$ days, and the most frequent symptom was pericarditic chest pain (83\%). Respectively, 50 and 33\% of patients presented after the second and the third dose of the vaccine. Almost all patients were treated with both nonsteroidal anti-inflammatory drugs and colchicine. Five patients (21\%) experienced a recurrence of pericarditis. No patient died or developed constrictive pericarditis. Mean follow-up was $8.0 \pm 3.2$ months.

\textbf{Conclusion} COVID-19 vaccine-related pericarditis typically manifest with mild clinical signs, in young male individuals, a few days after the second or third vaccine dose and are commonly characterized by a rapid complete recovery.

J Cardiovasc Med 2022, 23:779–783

\textbf{Keywords:} coronavirus disease 2019, pericarditis, vaccination

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Received 15 June 2022 Revised 26 July 2022 Accepted 8 August 2022

\textbf{Introduction} Acute pericarditis is an inflammatory pericardial syndrome defined by the presence of two or more of the following features: chest pain, pericardial friction rub, diffuse concave upward ST-elevation or PR depression on ECG and new or worsening pericardial effusion. Myopericarditis is defined as the presence of acute pericarditis with elevation of troponin and/or new or presumed new focal or global left ventricular systolic dysfunction. Myocardial involvement is usually confirmed noninvasively by cardiac magnetic resonance. \textsuperscript{1} The incidence of acute pericarditis has been reported as 27.7 cases per 100,000 population per year and is responsible for 0.1\% of all hospital admissions. \textsuperscript{2}

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic that has affected the lives of billions of individuals worldwide. In the absence of effective therapies against SARS-CoV-2, vaccination is crucial to limit the pandemic spread of COVID-19 and reduce mortality. Clinical trials demonstrated that the COVID-19 vaccines are both well tolerated and effective and no clinical trial has reported major cardiovascular events, including pericarditis. \textsuperscript{3,4} Due to these findings, the European Medical Agency has authorized four vaccines to prevent COVID-19 [Comirnaty (BNT162b2), Jcovden (Ad26.COV2-S), Spikevax (mRNA-1273), Vaxzevria (AZD1222)] and the vaccination campaign began in Italy, as in all Europe on the 27 December 2020.

Several cases of vaccine-related myocarditis have been reported in literature; however, there is a paucity of information regarding pericarditis and events after the third vaccination dose.

\textbf{Methods} We included all consecutive patients admitted with pericarditis following SARS-CoV-2 vaccination to the Cardiology Department of the University Hospital of Udine, between 1 April 2021 and 15 April 2022. The time interval between vaccination and the onset of pericarditis symptoms had to be less than 15 days (independently from the dose). \textsuperscript{5}

Acute pericarditis and myopericarditis were diagnosed by the 2015 European Society of Cardiology guidelines for the diagnosis and management of pericardial diseases\textsuperscript{1} and all patients had negative reverse transcription–PCR of nasopharyngeal swabs for SARS-CoV-2.
Baseline characteristics of study patients were summarized as frequencies and percentages for categorical variables and median ± range/interquartile range (IQR) for continuous variables. As an exploratory analysis, we compared clinical characteristics between patients with acute pericarditis and myopericarditis.

Fisher’s exact test was used for categorical variables and unpaired Student’s t-test or Mann–Whitney U test for continuous variables. A two-tailed P less than 0.05 was considered statistically significant.

Results
Details are provided in Table 1. Nineteen (79%) male and five (21%) female patients diagnosed with pericarditis after receiving COVID-19 vaccination were included. The mean age was 39.7 ± 19.8 years. Eleven (46%) patients had acute pericarditis and 13 patients had myopericarditis. Patients who developed myopericarditis were younger (26 vs. 55 years, P < 0.001), had fewer comorbidities (no comorbidities in 92 vs. 45%, P = 0.02) and more frequently had a history of previous pericarditis (38 vs. 0%) than those who developed acute pericarditis. Overall, four were active or former smokers, and the most common comorbidity was hypertension (25% of patients). One patient experienced a recurrence 11 months after mild pericarditis related to SARS-CoV-2 infection; four patients relapsed after previous idiopathic pericarditis (mean time 21.2 ± 7.3 months). One patient developed pericarditis after AZD1222 vaccination, all others (96%) after mRNA vaccines. Most patients developed pericarditis after the second or the third dose of vaccine (50 and 33%, respectively). The mean time between vaccination and symptoms onset was 7.0 ± 4.9 days and the most frequent symptom was pericarditic chest pain (83%) followed by fever and dyspnea. The most common abnormal ECG finding was diffuse ST-elevation and PR depression (63%, most frequent in acute pericarditis). All patients with definitive myopericarditis underwent cardiac magnetic resonance within 15 days from clinical presentation, which confirmed the clinical diagnosis. No patient underwent endomyocardial biopsy because of stable and uncomplicated cases with myocardial involvement. Pericardial effusion was found in 11 (46%) patients and was reported as mild in 8 patients. No patient needed pericardial drainage. Four patients with myopericarditis had mild reduction of LVEF at presentation and during follow-up. The median values of C-reactive protein were 60 mg/l. Most patients (75%) were treated with dual therapy, and the most used drugs were colchicine and ibuprofen (88 and 83% of patients, respectively). All patients with myopericarditis and six patients with acute pericarditis were hospitalized with a median length of stay of 4.2 ± 2.6 days. Four patients developed a recurrence of pericarditis and one received anakinra after failure of therapy with nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, and prednisone. Mean follow-up was 8.0 ± 3.2 months.

Discussion
Historically, postvaccination myocarditis and pericarditis have been reported as a rare adverse event, especially after live-attenuated smallpox vaccine and less frequently for diphtheria, poliomyelitis, tetanus, influenza and hepatitis B.7,8 Although acute pericarditis and myopericarditis were not observed as adverse events in coronavirus disease 2019 vaccine trials,9 suspected cases have been reported following vaccination, particularly in adolescents and young adults.9,10

In this article, we summarize 24 cases of COVID-19 vaccine-related pericarditis and discuss their association with the vaccination.

The average number of pericarditis observed every 3 months during the vaccine period was significantly higher than during the prevaccination period (12.3 ± 0.8 vs. 6.2 ± 1.9, P < 0.001) (Fig. 1).

In our cases, young healthy men (<40 years old) were at higher risk of developing pericardial and myocardial inflammation after COVID-19 vaccination, and this was consistent with the literature.11,12

This result could be because of increased levels of inflammatory cytokines at puberty, and the sex difference may be explained by the pro-inflammatory role of testosterone in male individuals, as opposed to the anti-inflammatory role of estrogen in female individuals.13

This pro-inflammatory state also appears to be the cause of the severe hyper-inflammation condition (i.e. Multi-system Inflammatory Syndrome in Children), which has been described in children, within 2–4 weeks of SARS-CoV-2 infection. This syndrome can result in a severe clinical course requiring intensive care management with a mortality rate of 1–2%.14

The typical onset of symptoms, usually after the second or third dose of the vaccine (83% of our patients), suggests an immune-mediated mechanism because of an important cytokine activation of preexisting auto-reactive immune cells.15 In this regard, it could be interesting to consider an assessment of serological evidence for prior SARS-CoV2 infection, especially in young subjects with pericarditis after the first dose. Furthermore, in our patients, the average time between the second and third dose of vaccine was less than 6 months (5.3 ± 0.8), and this short time between doses, in susceptible individuals, may have promoted the above exaggerated autoimmune response.

As for idiopathic or virus-related pericarditis, the common clinical presentation was chest pain16 and the most frequent ECG abnormality was widespread ST-segment elevation with PR depression. ECG changes were not associated with a worse prognosis.17
According to the literature,18 these inflammatory heart diseases appear to be a typical adverse event following mRNA vaccines (96% of our patients) compared with the recombinant adenovirus vector-based vaccine (only one patient in our series).

Although the exact mechanism underlying mRNA vaccine-related pericarditis is poorly understood, it has been proposed that, in the presence of a genetic predisposition, the otherwise less immunogenic modified spike protein-coding mRNA molecule used in the vaccine is detected...
as antigen. This leads to activation of an aberrant immune system response resulting in a pro-inflammatory cascade.15

For this reason, extreme caution is required in administering the vaccine to chronically immunosuppressed subjects and in those with immune-mediated diseases or a recent history of pericarditis (4, 13 and 21% of our patients, respectively). In our cases, a patient known for previous postviral pericarditis and celiac disease, developed myocarditis 14 days after the second dose of the vaccine and 37 days after the third one.

Other possible mechanisms could be a molecular mimicry between the spike protein of SARS-CoV-2 and self-antigens19 (i.e. a cross-reaction between antibodies against SARS-CoV-2 spike glycoproteins and α-myosin has been experimentally demonstrated) or a nonspecific innate inflammatory response.20

All patients diagnosed with myocarditis underwent cardiac MRI within 15 days from clinical presentation and tissue characterization using T1 and/or T2 mapping was suggestive for acute myocarditis in all cases.21,22 No patient underwent endomyocardial biopsy as all myocarditis appeared transient and self-limited.23

We found pericardial effusion in 11 (46%) patients and was reported as large only in one patient. As in previous reports, pericardial effusion does not seem related to the severity of the pericarditis, unlike what happens in COVID-19 patients in which it appears related to poor prognosis.24

No data are available on specific treatment for vaccine-associated pericarditis; however, favorable evolution with prompt resolution of symptoms has been reported in most cases. The most commonly used therapeutic strategy includes anti-inflammatory drugs and guided medical therapy if left ventricular function is reduced. In tachycardic patients, beta-blocker drugs may also improve symptoms by slowing heart rate.25

In our case series, four patients were treated with only one anti-inflammatory drug and almost all others were treated with the mainstay therapy for acute myocarditis:1 the combination therapy with colchicine and NSAIDs. Overall, short-term clinical outcomes have been favourable, without relevant arrhythmias and with rapid complete recovery. No patient developed cardiac tamponade, only four patients had a recurrence of pericarditis and one (already known for autoimmune disease) received anakinra after failure of therapy with NSAIDs, colchicine and prednisone.

These findings seem to confirm the mild clinical course of this condition and support the effectiveness of evidence-based therapy for acute myocarditis in this setting as well.

**Limitations**

First, the study was composed of a small sample of a single large center, limiting the generalizability of the results. Second, it is an observational study, thus prospective studies with larger patient cohorts are needed to confirm our findings. Third, temporal association does not...
prove causation, although the short time span between vaccination and pericarditis onset strongly supports the possible relationship. Fourth, although all published studies had reported clinical outcomes in the short term, the mid-term to long-term prognosis remains unknown.

Conclusion
We report 24 cases of pericarditis after COVID-19 vaccination. Most cases were in young healthy male individuals, within a few days after the second or third vaccination, typically with mild clinical signs and were commonly self-limited. In conclusion, despite these rare side effects, the benefits of COVID-19 vaccination clearly outweigh the limited risk of pericarditis and myocarditis, and vaccination is strongly recommended to prevent COVID-19 infection, transmission and related complications.

Conflicts of interest
There are no conflicts of interest.

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