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Short communication

A case series of acute pericarditis following COVID-19 vaccination in the context of recent reports from Europe and the United States

George Lazaros,a,* Cleo Anastassopoulou,b,1 Sophia Hatziantoniou,c Theodoros Kalos,a Stergios Soulaidopoulos,a Emilia Lazarou,a Charalambos Vlachopoulos,a Dimitrios Vassilopoulos,d Athanasios Tsakris,b,1 Costas Tsioufis,a

a First Cardiology Department, School of Medicine, Hippokration General Hospital, National and Kapodistrian University of Athens, Athens, Greece
b Department of Microbiology, Medical School, National and Kapodistrian University of Athens, Athens, Greece
c Laboratory of Pharmaceutical Technology, Department of Pharmacy, School of Health Sciences, University of Patras, Patras, Greece
d Second Department of Medicine and Laboratory, Clinical Immunology-Rheumatology Unit, School of Medicine, Hippokration General Hospital, National and Kapodistrian University of Athens, Athens, Greece

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1. Introduction

1.1. Background

Acute pericarditis (AP) is the most common form of inflammatory heart disease with an estimated annual incidence of approximately 28 cases/100,000 subjects in the Western world [1]. The most common underlying etiology is a definite or presumed viral infection. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as a novel etiologic agent of a variety of pericardial syndromes, including AP.

In the absence of an efficacious therapeutic against SARS-CoV-2, mass vaccination currently represents the exclusive means to control the outbreak. Several highly effective vaccines at preventing coronavirus disease 2019 (COVID-19) hospitalizations and deaths and potentially reducing SARS-CoV-2 transmission, became available and were granted emergency use authorization in record time. A number of rare vaccine-related complications have been reported. In this case series, we describe AP as a possible complication following COVID-19 vaccination, focusing on the time interval between vaccination and symptoms onset, clinical manifestations, peculiar features and short-term outcomes.

1.2. National COVID-19 vaccination scheme

The mass vaccination program started in Greece on the 27th of December 2020. By June 21, 2021, over 7.1 million subjects had received at least one vaccine dose, with ~3.1 million (30.5% of the population) having completed the recommended scheme [2,3]. Available vaccines during the observation period (December 27, 2020 to June 21, 2021) included Pfizer-BioNTech's BNT162b2 (Tozinameran, Comirnaty, 5,145,028 administered doses) and

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Modernas mRNA-1273 (Spikevax, CX-024414, 717,403 doses) mRNA vaccines (82.2% of total administered doses), as well as the adenovirus (Ad)-vected AZD1222 (Covishield or Vaxzevria, ChAdOx1-S, Oxford-AstraZeneca, 1,092,223 doses) and Janssen (Johnson & Johnson) (Ad26.COV2.S, 177,025 doses).

1.3. Patients

All consecutive cases of AP between January and July 2021 temporally associated with COVID-19 vaccination that presented to our hospital, a referral center for the diagnosis and treatment of pericardial diseases from an urban area of approximately 3 million inhabitants, were recorded. In total, 9 consecutive events of AP in 8 patients following COVID-19 vaccination were recorded and reported to our national Medicines and Healthcare Products Regulatory Agency. The diagnosis of AP was based on the criteria proposed by the 2015 European Society of Cardiology (ESC) guidelines for the diagnosis and management of pericardial diseases [1]. All patients had negative RT-PCR for SARS-CoV-2. Alternative etiologies underlying pericarditis were excluded upon meticulous diagnostic work up [1].

2. Results

2.1. Vaccine platforms and types

Details on the aforementioned cases are presented in Table 1. AP occurred after vaccination with BNT162b2 (6/9 events), AZD1222 (2/9 events) and mRNA-1273 (1/9 events).

2.2. Vaccine dose and symptom onset

Pericarditis developed either after the first (five events), or the second dose (four events). The median (IQR) time between vaccination and symptoms onset was 7 (3–23) days (range 2–38 days). Interestingly, in one patient (event #5 and #6 in Table 1) AP developed 12 days after the first dose and recurred 30 days after the second one.

2.3. Clinical features

In the present case series, unlike viral pericarditis, women were affected slightly more often than men (five vs. three) and the mean age of the patients was 65.8 ± 10.2, which is higher compared to viral AP. The latter observation may reflect the older individuals’ prioritization for vaccination. No striking differences were observed between vaccine-related and acute (non-vaccine related) pericarditis. Chest pain was the most common presenting symptom followed by dyspnea. It should be emphasized that troponin was negative in all cases since only patients without myocardial involvement and normal ejection fraction were assessed. Fever was observed in three events (two patients). In no instance did ECG depict S-T segment elevation. In the two cases with large effusions low voltage and electrical alternans was observed (Fig. S1). Pericardial effusion was noted in all cases. In four events a large-sized effusion was found, occasionally with unusual distribution (Fig. 1, which in (half of them) accounted for cardiac tamponade. The burden of systemic inflammation as depicted by serum C-reactive protein (CRP) values was quite high (mean values 135.1 ± 106.6 mg/L). Cardiac MRI was not routinely performed since according to the ESC guidelines, in the absence of troponin elevation, it is considered only a confirmatory finding for the diagnosis of AP and reserved for doubtful/atypical cases. In event #7 (a patient with a history of pericarditis in stable remission for two years without treatment), cardiac MRI depicted pericardial edema and late gadolinium enhancement suggestive of AP (Fig. S2).

2.4. Treatment and outcome

Details on patients’ comorbidities and chronic medical treatment are provided in Table S1. AP treatment was based on the pertinent guideline recommendations and included aspirin, non-steroidal anti-inflammatory drugs, glucocorticoids and anakinra [1]. Two patients (4# and 9#) underwent pericardiocentesis due to cardiac tamponade. The former patient subsequently underwent partial pericardietomy through median sternotomy since pericardial evacuation was partial due to pericardial septa and the persistence of symptoms and hemodynamic impairment. Notable constrictive physiology was detected after the above-mentioned interventions, which, nonetheless, reversed promptly with glucocorticoids. Pericardial fluid analysis and pericardial histology did yield non-specific findings. In contrast, in patient #9 symptoms regressed promptly after pericardiocentesis. No death and no further complications were observed, although the follow-up was relatively short.

3. Discussion

AP refers to the inflammation of the pericardium, the fibroelastic tissue surrounding the heart, that is caused by infections or mediated by autoimmune/autoinflammatory mechanisms [1]. It is most often encountered in men aged 16–65 years [1]. Sex hormones, i.e. testosterone, may account for the predisposition of males to acute viral pericarditis through a more intense inflammatory response [4].

Our cohort of patients notably included more women than men and the overall patients’ age was higher compared to AP. The median (IQR) time between vaccination and symptoms onset in this cohort was 7 (3–23) days, which is longer yet with a shorter upper range limit than previously reported [3 days (0–33) after dose 1 and 2 days (0–80) after dose 2], in the younger US cohort [5]. Pericarditis recurrence after the second dose in event #6 may be perceived as a positive rechallenge, which is strongly indicative of a cause-effect relationship. However, since pericarditis may recur in 15–30% of cases after a first episode, a causal link to vaccination might be questioned or at least is not definite [1].

The occurrence of pericarditis after immunization is extremely rare [6]. Few cases of pericarditis have been reported after immunization against influenza and hepatitis B virus [6]. For the SARS-CoV-2 vaccines, reports of pericarditis as of June 18–19 in the European Economic Area (EEA), which includes 27 European Union (EU) countries and Iceland, Liechtenstein and Norway, and in the United States are presented in Table 2. Based on the combined results from the EEA and the US, incidence rates sum up to: 670/392,769,904 doses, or 1.71/mi doses (BNT162b2), 317/158,247,931 doses, or 2.00/mi (mRNA-1273), 45/18,193,523 doses, or 2.47/mi (Ad26.COV2.S) and 128/49,148,046 million doses, or 2.60/mi (AZD1222), or 987/551,017,835 doses, or 1.79/mi doses) for mRNA vs. 173/67,341,569 doses (2.57/mi doses) for ad-vectored vaccines, and an overall rate of 1.88 cases/mi vaccine doses.

Our analysis confirms the rarity of pericarditis as a presumably adverse effect post COVID-19 vaccination. Although initial reports from Israel implicated BNT162b2 in myocarditis/pericarditis, our data indicate that this complication may also appear with other vaccines. In our cohort, cases were in analogy to nationally administered doses by vaccine type (72.1% BNT162b2, 15.3% AZD1222, 10.1% mRNA-1273, and 2.5% for the recently approved Ad26.COV2.S), probably suggesting that the pathogenesis of pericarditis
following COVID-19 vaccination is not specifically related to the properties of an individual vaccine. Regarding the age of pericarditis cases post COVID-19 vaccination, EEA data showed that most cases occur in the working age
group (18–64 years). The detailed US data that include five categories for the working age group clearly indicate that pericarditis cases occur more frequently among young adults, and especially among 18–29-year-old subjects. However, 48/313 such potential adverse events were in subjects < 18 years (with 45/48 in males), where data are beginning to accumulate. At present (in late September 2021 during manuscript revision), BNT162b2 is approved for use in adults and adolescents aged 16 and above and authorized for emergency use in children aged 12–15 in Europe and the US, while an extension of indication for use in children aged 5–11 is anticipated. Moderna’s mRNA-1273 that is currently available for adults over 18 years of age is expected to follow with similar extensions to adolescents and children.

Pericarditis post COVID-19 vaccination appears to be more common among men for mRNA vaccines and Ad26.COV2.S. Intriguingly, this complication was detected more frequently among women, particularly of the working age group, after AZD1222 (77 vs. 48 of 128 pericarditis cases overall, Table 2a. Regarding outcome, most patients recovered/are recovering, few had a complicated disease course, whilst four fatalities due to complicated pericarditis were recorded overall following vaccination with mRNA vaccines. Thus, although rare, the potential association of COVID-19 with pericarditis could be serious.

Both Ad26.COV2.S and AZD1222 consist of a recombinant replication-incompetent human (type 26) or simian (chimpanzee) adenovirus vector, respectively, encoding the SARS-CoV-2 spike protein [9,10]. Adenoviruses can infect the pericardium and cause pericarditis. In the case of vaccination with ad-vectorized vaccines, the adenoviruses (backbones) cannot replicate, but they can hypothetically infect the pericardium, allowing for the expression of the spike protein to extremely high levels, since $5 \times 10^{10}$ viral particles are contained in each vaccine; the result may be acute toxicity through the activation of innate immune responses, as described in the literature [9–11].

Innate immune responses leading to inflammatory reactions may also be triggered by extra RNA species contained in mRNA vaccines, stemming either from the initial stages of the manufacturing procedure, or from suboptimal late stage manufacturing and/or storage conditions in conjunction with the inherent instability of the RNA molecule, as recently described [12]. Namely: (i) During the in vitro transcription both single-stranded (ss) and double-stranded (ds) RNA may be present as by-products, which may be recognized by innate immune sensors, such as toll-like receptors and cytoplasmic protein kinases [12]. The modification of the nucleotide composition of the RNA to contain N1-methylpseudouridine instead of uridine minimizes, but probably does not eliminate such undesired immune responses. (ii) Despite the encapsulation of the mRNA in lipid nanoparticles (LNPs), degradation of the mRNA-LNP moiety can occur, particularly under non-recommended (ultra-frozen) storage conditions, or possibly as vaccine batches are thawed for administration. Some early commercial batches of BNT162b2 that was the first to receive approval were found to contain lower than expected levels of intact mRNA [12]. Hence, good manufacturing practices should be followed meticulously, importantly for the purification of the mRNA from in vitro transcription contaminants and for the quality control assurance of each vaccine dose. Improvements in the mRNA-LNP product stability are warranted so as to prevent even such rare adverse events potentially associated with vaccination.

To date, just two cases of vaccine-related pericarditis have been reported [13]. To the authors’ knowledge, this is the first case series which systematically assessed AP presumably related to SARS-CoV-2 vaccination. The latter entity apparently shares several features with the typical (viral) AP. However, a non-negligible rate of
cardiac tamponade needing emergent pericardiocentesis was observed (2 out of 9 events, 22%) which is higher than the respective rate in AP namely 1.2% in viral pericarditis and 20.2% in AP of specific etiology [14]. In this context, a better characterization of pericarditis following vaccination is needed; it should be judicious for these patients to be closely monitored for response to treatment and potential complications.

Finally, a very important point that has yet to be clarified concerns the exact time interval during which a cause-effect relationship between vaccination and pericarditis is presumable. In the presented cases, this period was arbitrarily set to 6 weeks. This time period seems reasonable based on available data and on the established knowledge linking vaccines with autoimmune conditions [15,16]. Unfortunately, in the absence of a national AP
registry we were not able to estimate the number of the expected cases of AP for the same time period. Nonetheless, this estimation is per se difficult, taking into consideration that according to the most recent ESC guidelines only ~15% of AP cases with high-risk criteria require hospitalization [1]. This is theoretically traduced in difficulties in data collection and monitoring.

4. Conclusion

Although AP is emerging as a potential rare adverse effect after COVID-19 vaccination, every effort should be made to avoid sensationalist statements not supported by solid evidence, which may undermine mass vaccination.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.09.078.

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