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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



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ABSTRACT

Background: COVID-19 vaccines were efficacious and safe in clinical trials. We report nine events of acute pericarditis (AP) in eight patients following COVID-19 vaccination with BNT162b2 (6/9), AZD1222 (2/9) and mRNA-1273 (1/9).

Methods: All patients were referred for AP temporally linked with COVID-19 vaccination. Chest pain was the most common clinical manifestation. Alternative etiologies were excluded upon thorough diagnostic work up. AP diagnosis was established according to ESC guidelines.

Findings: Five events occurred after the first vaccine dose and four after the second. The mean age in this cohort was 65.8 ± 10.2 years and the men/women ratio 3/5. All events resolved without sequelae; two events were complicated by cardiac tamponade requiring emergent pericardial decompression. Hospitalization was required in four cases.

Interpretation: Although causality cannot be firmly established, AP has emerged as a possible complication following COVID-19 vaccination. Further investigation is indispensable to fully characterize this new entity.

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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 of 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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Moderna's mRNA-1273 (Spikevax, CX-024414, 717,403 doses) mRNA vaccines (82.2% of total administered doses), as well as the adenovirus (Ad)-vectored 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 pericardiectomy 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 (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 (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

Table 1
Details on patients' demographics, clinical features, treatment and outcome.

	Event #1	Event #2	Event #3	Event #4	Event #5	Event #6	Event #7	Event #8	Event #9
Age (years)	61	74	72	57	76	76	70	46	61
Sex	Male	Female	Male	Female	Male	Male	Female	Female	Female
Vaccine type	AstraZeneca	Pfizer	Pfizer	Pfizer	Pfizer	Pfizer	Moderna	Pfizer	AstraZeneca
Dose given	First	Second	First	Second	First	Second	Second	First	First
Time from vaccine to symptoms (days)	16	3	4	7	12	30	38	2	3
History of pericarditis	No	No	No	No	No	No	Yes	Yes	No
History of COVID-19	No	No	Yes (11/20/20)	No	No	No	No	No	No
Hospitalization (days)	No	No	Yes (4)	Yes (9)	Yes (5)	No	No	No	Yes (5)
Follow-up (days)	80	50	25	25	90	90	17	25	26
Clinical manifestations									
Chest pain	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Dyspnea	No	No	Yes	Yes	No	No	No	No	Yes
Fever	No	No	38 °C	No	39 °C	38 °C	No	No	No
Pericardial rubs	No	No	No	No	No	No	Yes	No	No
Heart rate	90	85	80	135	90	78	80	75	112
Arterial blood pressure (mmHg)[§]	135/85	120/80	120/75	110/80	130/80	125/80	115/75	110/80	110/70
Pulsus paradoxus	No	No	No	Yes (by 15 mmHg)	No	No	No	No	Marginal (by 10 mmHg)
Selected laboratory findings									
Peak CRP (NV < 5 mg/L)	320.4	50.8	280.1	142.6	138.5	159.3	49.4	63.3	11.5
Hs-TnI (pg/ml)[*]	8.3	2.8	10.2	13.5	0.6	NA	5.99	0	1.9
ECG	NSF	NSF	NSF	Low voltage, electrical alternans	NSF	NSF	NSF	NSF	Low voltage, electrical alternans
Pericardial effusion	Moderate (1.2 cm)	Mild (0.9 cm)	Large (4 cm)	Large (2.1 cm)	Mild (0.5 cm)	Mild (0.4 cm)	Mild (0.3 cm)	Large (2.1 cm)	Large (4.3 cm)
Ejection fraction (%)	60	65	55	60	55	55	65	60	65
Cardiac tamponade	No	No	No	Yes	No	No	No	No	No
Medical treatment (daily dose)^{**}									
	Ibuprofen 1.8gr then MPdn 24 mg due to intolerance	Ibuprofen 1.8gr	Prednisolone 15 mg	MPdn 32 mg	Ibuprofen 1.8gr	Ibuprofen 1.8gr and then MPdn 24 mg	Aspirin 3gr	Anakinra 100 mg on alternate days	Colchicine, paracetamol
Interventions									
Pericardiocentesis	No	No	No	Yes	No	No	No	No	Yes
Surgical decompression	No	No	No	Yes (due to incomplete evacuation and persisting symptoms)	No	No	No	No	No
Outcomes									
Pericarditis recurrence	No	No	No	No	Yes	No	No	No	No
Death	No	No	No	No	No	No	No	No	No
Constrictive pericarditis	No	No	No	Yes (transient constrictive physiology emerged after pericardiocentesis)	No	No	No	No	No

In all cases PCR for SARS-CoV 2 and serum h-TnI were negative. Similarly, no alternative etiology for acute pericarditis was found during work up. Details on comorbidities, chronic medical treatment, treatment at baseline and medical treatment. * NV < 14 in females and < 34 in males. **All patients received colchicine 0.5 twice daily. [§]Last follow-up by the end of June.

Events #5 and #6 refer to the same patient reporting clinical data relevant to the first attack (#5) and first recurrence (#6).

CRP = C reactive protein, NV = normal values, ECG = electrocardiogram, COVID-19 = coronavirus disease 2019, Hs TnI = high-sensitivity troponin I, NSF = Non-specific findings, MPdn = methylprednisolone.

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

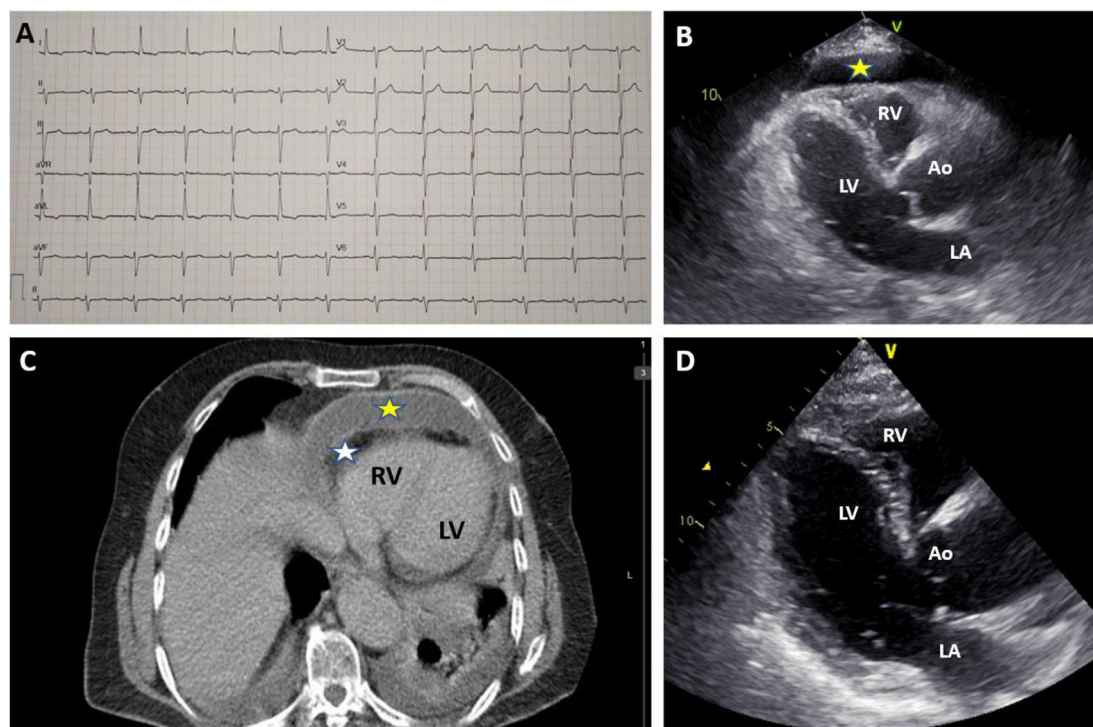


Fig. 1. Event #3. **Panel A:** Admission ECG depicting sinus rhythm at a rate of ~80 bpm with left anterior hemiblock and non-specific repolarization abnormalities. **Panel B:** Admission echocardiographic study, slightly modified parasternal long axis view showing large anteriorly located pericardial effusion. **Panel C:** Admission chest CT scan highlighting a large effusion (~4 cm) adjacent to the right heart chambers (yellow star) and negligible amount of fluid in the remainder pericardial spaces. White star highlights epicardial fat. **Panel D:** Regression of pericardial effusion (same view with Panel B). Ao = ascending aorta, LA = left atrium, LV = left ventricle, RV = right ventricle. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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-vectored 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 5×10^{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 N^1 -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

Table 2
Description of pericarditis cases post COVID-19 vaccination in Europe and the United States.

2a. Description of pericarditis cases post COVID-19 vaccination reported in the European Economic Area (EEA)* by licensed vaccine platform and type.												
Total by platform	mRNA-based (N = 247,077,835)						Vector-based (N = 55,471,569)					
	BNT162b2			mRNA-1273			Ad26.COVS.2.S			AZD1222		
Vaccine	219,489,904			27,587,931			6,323,523			49,148,046		
Total (N) by type												
Age group	Sex											
	♀	♂	Total	♀	♂	Total	♀	♂	Total	♀	♂	Total
Not specified	14	19	33	1	2	3	0	0	0	5	3	8
12–17 years	1	7	8	0	0	0	0	0	0	0	0	0
18–64 years	115	92	207	25	50	75	0	0	0	63	35	98
65–85 years	39	53	92	17	14	31	5	9	14	9	8	17
> 85 years	3	7	10	2	0	2	1	1	2	0	2	2
Total	172	178	350	45	66	111	6	10	16	77	48	125
Outcome**	Number of individual cases											
Fatal	1			1			0			0		
Complicated course	74			40			5			41		

2b. Description of pericarditis cases post COVID-19 vaccination reported in the United States by licensed vaccine platform and type.												
Total by platform	mRNA-based (N=303,940,000)						Vector-based					
	BNT162b2			mRNA-1273			Ad26.COVS.2.S			AZD1222		
Vaccine	173,280,000			130,660,000			11,870,000					
Total (N) by type												
Age group	Sex											
	♀	♂	Total	♀	♂	Total	♀	♂	Total	♀	♂	Total
Unknown	2	4	6	3	5	8	0	0	0	0	0	0
6–17 years	3	45	48	0	0	0	0	0	0	0	0	0
18–29 years	8	72	80	15	52	67	1	8	9	1	8	9
30–39 years	14	31	45	10	20	30	3	2	5	3	2	5
40–49 years	17	15	32	10	12	22	0	3	3	0	3	3
50–59 years	20	23	43	7	14	21	3	3	6	3	3	6
60–64 years	12	6	18	10	9	19	0	2	2	0	2	2
65–79 years	17	19	36	13	17	30	2	1	3	2	1	3
>80 years	4	1	5	4	3	7	0	0	0	0	0	0
TOTAL	97	216	313	72	132	204	9	19	28	9	19	28
Outcome*												
Fatal	0			0			2			0		
Complicated course	52			83			135			42		

2c. Pericarditis cases post COVID-19 vaccination reported in the European Economic Area (EEA) and the United States of America (USA) by vaccine platform and type normalized per million vaccine doses.				
Vaccine	BNT162b2	mRNA-1273	Ad26.COVS.2.S	AZD1222
EEA				
Cases/mi doses	1.613	4.023	2.530	2.604
Total by platform	mRNA: 1.882		Vector: 2.596	
USA				
Cases/mi doses	1.824	1.577	2.443	NA
Total by platform	mRNA: 1.717		Vector: 2.443	
TOTAL (EEA+USA)				
Cases/mi doses	1.706	2.003	2.473	2.604
Total by platform	mRNA: 1.791		Vector: 2.569	

* The EEA includes 27 European Union (EU) countries (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden), and also Iceland, Liechtenstein and Norway.

** Only severe outcome categories are included for clarity.

Data (through June 19, 2021) for complete entries summarized from: European Medicines Agency, EudraVigilance-European database of suspected adverse drug reaction reports and European Centre for Disease Prevention and Control, COVID-19 Vaccine Tracker. Available at: <https://www.adrreports.eu> and <https://vaccinetracker.ecdc.europa.eu/>, respectively [2,7].

* Only severe outcome categories are included for clarity.

Data (through June 18, 2021) for complete entries summarized from: Vaccine Adverse Event Reporting System. Available at: <https://vaers.hhs.gov/data.html> [8]. Data on administered vaccine doses were retrieved from <https://ourworldindata.org/coronavirus> [3].

NA, Not Applicable. AZD1222 is not approved for use in the United States.

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 translated 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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