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A case series of acute myocarditis associated with SARS-CoV-2 mRNA vaccination

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Summary

We present three cases of patients who devel-oped acute, non-severe myocarditis following messenger RNA-1273 vaccine from Moderna (Moderna Inc.) against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A brief review of the literature, diagnostic modalities, work-up and treatment are discussed.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has led to an unprecedented manufacturing of vaccines against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The two preparations used in Switzerland (messenger RNA [mRNA]-1273 vaccine from Moderna (Moderna Inc.) and BNT162b2 vaccine from Pfizer-BioNTech (Pfizer Inc.; BioNTech SE) are the first of their kind and consist of a lipid nanoparticle-encapsulated mRNA-based vaccine that encodes the prefusion-stabilised full-length spike protein of SARS-CoV-2. Phase III trials reported outstanding efficacy and very few adverse effects. In particular, no cases of myocarditis were identified (30'420 volunteers in the mRNA-1273 group and 43'548 in the BNT162b2 one) [1, 2].

Case descriptions

Patient 1

Urgent coronary angiography was performed in a 20-year-old male who presented with on-going chest pain for the preceding 6 hours. The patient had no significant medical history and was a regular cannabis consumer. Three days earlier, he received the second dose of the Moderna vaccine against SARS-CoV-2. The next day, he suffered from fever, chills, nausea and vomiting. The patient was afebrile, stable and in mild distress, with physical examination being unremarkable. Figure 1 depicts the 12-lead electrocardiogram (ECG). Coronary angiography revealed normal coronary arteries (videos 1–3). Relevant laboratory findings were: high-sensitive cardiac troponin T (hs-cTnT) 607 ng/l (normal value: <14 ng/l), creatine kinase (CK) 529 U/l, N-terminal pro-B-type natriuretic peptide (NT-proBNP) 328 ng/l (normal value: <300 pg/ml), C-reactive protein (CRP) 28 mg/l. A nasopharyngeal swab test with real-time reverse transcriptase polymerase chain reaction (RT-PCR) was negative for SARS-CoV-2. Left ventricular ejection fraction (LVEF) on transthoracic echocardiography (TTE) performed on admission was 55% with apical hypokinesia (videos 4–8). An angiotensin-converting enzyme inhibitor (ACEi) was initiated.

Cardiac enzymes peaked on day 2 (hs-cTnT 1139 ng/l and CK 786 U/l).

On day 3, cardiac magnetic resonance imaging (CMR) showed two areas of marked subepicardial late gadolinium enhancement (LGE), in basal to mid, and apical lateral walls, with signs of inflammation/oedema on dedicated sequences (short-tau inversion recovery [STIR]), and minimal pericardial effusion (fig. 2A, B, C).

The patient was discharged on day 4 on lisinopril 10 mg once daily (OD).

Patient 2

A 45-year-old healthy male presented with on-going chest pain for the preceding 4 hours. Three days before, he had received the second dose of the Moderna vaccine against SARS-CoV-2, following which he had been feeling unwell and developed fever and chills. The patient was stable, compensated and afebrile. Physical examination was unremarkable. Figure 3 depicts his 12-lead ECG. Relevant laboratory findings were: hs-cTnT 214 ng/l, CK 215 U/l, NT-proBNP 692 ng/l, CRP 42 mg/l. A nasopharyngeal swab tested with RT-PCR was negative for SARS-CoV-2. TTE showed a LVEF of 45–50% with diffuse hypokinesia and no pericardial effusion (videos 9–11). The patient received intravenous aspirin 250 mg, subcutaneous fondaparinux 2.5 mg and lisinopril 5 mg OD.

Coronary angiography performed on the following day showed normal coronary arteries (videos 12–14). Peak hs-cTnT reached 398 ng/l and CK 329 U/l.

On day 3, CMR was performed. T2-weighted sequences (T2 map, STIR) showed inflammation/oedema in the mid lateral wall, along with subepicardial LGE in the mid to apical lateral and inferior walls (fig. 4 A, B).

The patient was discharged on day 5 on lisinopril 10 mg OD and metoprolol 50 mg twice daily.

Patient 3

A 21-year-old healthy male presented with acute onset chest pain. Two days earlier, he had received the second dose of Moderna vaccine against SARS-CoV-2, following

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which he developed flu-like symptoms and fever. The patient was afebrile and in no distress. Physical examination was unremarkable. The 12-lead ECG is shown (fig. 5). Relevant laboratory findings were: hs-cTnT 523 ng/l, CK 516 U/l, NT-proBNP 178 ng/l, CRP 94 mg/l. A nasopharyngeal swab tested with RT-PCR was negative for SARS-CoV-2. The patient was admitted and started on an ACEi.

TTE performed on the following day showed a normal LVEF (videos 15–19). CMR performed on the same day showed lateral wall subepicardial LGE (fig. 6A, B). Peak hs-cTnT reached 552 ng/l and CK 652 U/l.

The patient was discharged on day 3 on lisinopril 5 mg OD.

All three patients were asymptomatic and doing well at 1-month clinical assessment. A follow-up CMR was scheduled at 6 months. Restriction in physical activity was recommended until then. In the absence of significant physical workload, no restraint from working was advised in asymptomatic patients with preserved LVEF.

You will find the video files in the multimedia collection of Cardiovascular Medicine: https://cardiovascmed.ch/online-only-content.

Discussion

Myocarditis is an inflammation of the myocardium that has a wide aetiological spectrum, including infectious, toxic-related and/or immune-mediated [3]. Vaccine-associated myocarditis, triggered by an immune-mediated mechanism, has been described in the literature, particularly with smallpox vaccination [4]. However, mRNA vaccine-related myocarditis has only been recently described following vaccination against SARS-CoV-2.

The three presented patients were evaluated at the University and Hospital of Fribourg, Switzerland, between June and July 2021. All of them were healthy young males who developed systemic symptoms (fever, chills) closely following the second dose of Moderna vaccine against SARS-CoV-2. Chest pain developed within 48–72 hours. Work-up revealed acute myocardial injury and ECGs were suggestive of peri-myocarditis with PR segment depres-

Figure 1: : Patient 1: Initial 12-lead ECG showing sinus rhythm at 66 bpm with an incomplete right bundle branch block pattern and significant ST-segment elevation in leads II, III, aVF and from V4 to V6. ST segment depression and inverted T wave in leads aVR, V1 and V2 can be seen.

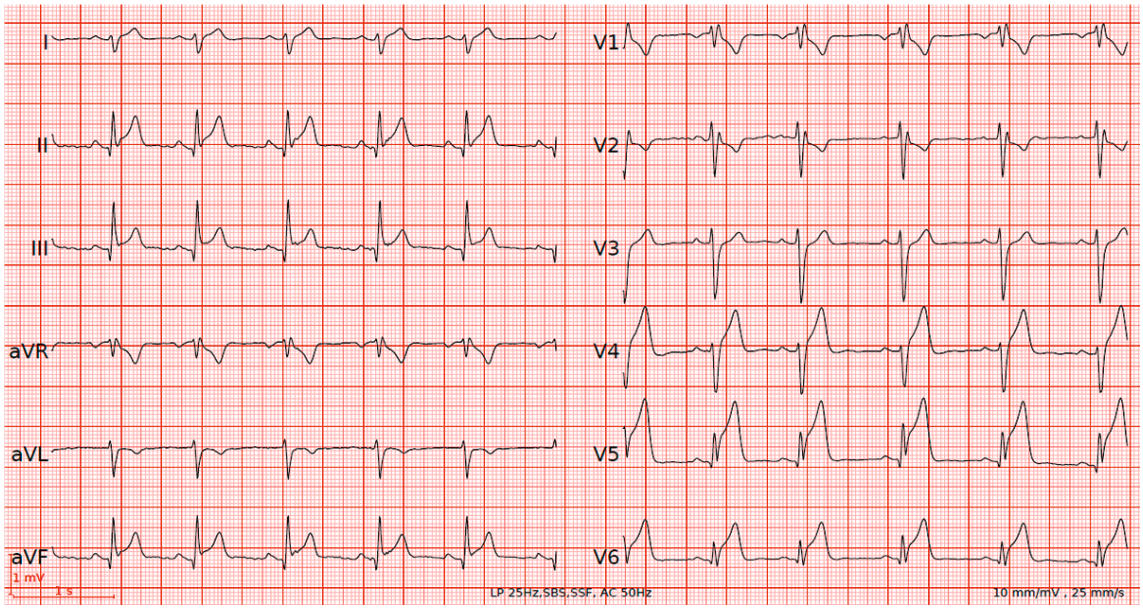
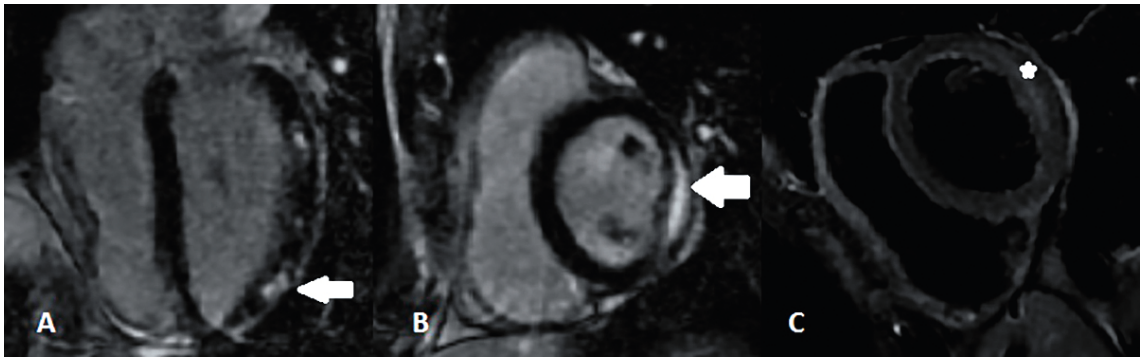


Figure 2: : Patient 1: Cardiac magnetic resonance imaging four chamber view (A) and short axis view (B) showing subepicardial late gadolinium enhancement in basal to mid, and apical lateral walls (white arrows), with inflammation/oedema in the same areas (white star) on short-tau inversion recovery sequences (C).



sion and diffuse ST segment elevation. Coronary angiography, performed in two out of the three patients to rule out an ST-segment elevation acute coronary syndrome (STE-ACS), was normal. TTE showed a preserved LVEF. Finally, CMR confirmed the diagnosis of myocarditis. Exclusion of an active SARS-CoV-2 infection at admission and temporal relationship between the second dose of vaccine and development of symptoms suggested a diagnosis of acute myocarditis induced by SARS-CoV-2 vaccination.

As of 16 August 2021, 306'293 doses of vaccine against SARS-CoV-2 had been administrated in the Canton of Fribourg, and the three cases described are the only ones diagnosed at the University and Hospital of Fribourg up to July 2021 [5]. The reported rate of vaccine-associated myocarditis in Switzerland is about 1/400'000 vaccine doses (first and second dose confounded), and it has been confirmed as a potential vaccination side effect by the Swiss Agency for Therapeutic Products (Swissmedic) [6]. According to the US Centers for Disease Control and Prevention (CDC), the overall incidence of myocarditis associated with SARS-CoV-2 mRNA vaccine in individuals aged 12 to 39 years old is 12.6/1'000'000 second-dose mRNA vaccinations (distribution shown in table 1). There was a net preponderance in younger individuals, with a median age of 26. Cases were more frequent in men than women (76% vs 24% respectively) and 76% of cases were diagnosed following the second dose, with a median symptom onset on day 3 [7, 8].

The exact pathophysiological mechanism of mRNA vaccine-related myocarditis is uncertain. Innate immune response seems to play a crucial role in the acute phase reaction following vaccination [8, 9]. Other proposed

Figure 3: : Patient 2: Initial 12-lead ECG showing a sinus rhythm at 64 bpm with diffuse concave ST-segment elevation, and subtle PR segment depression in the inferior leads.

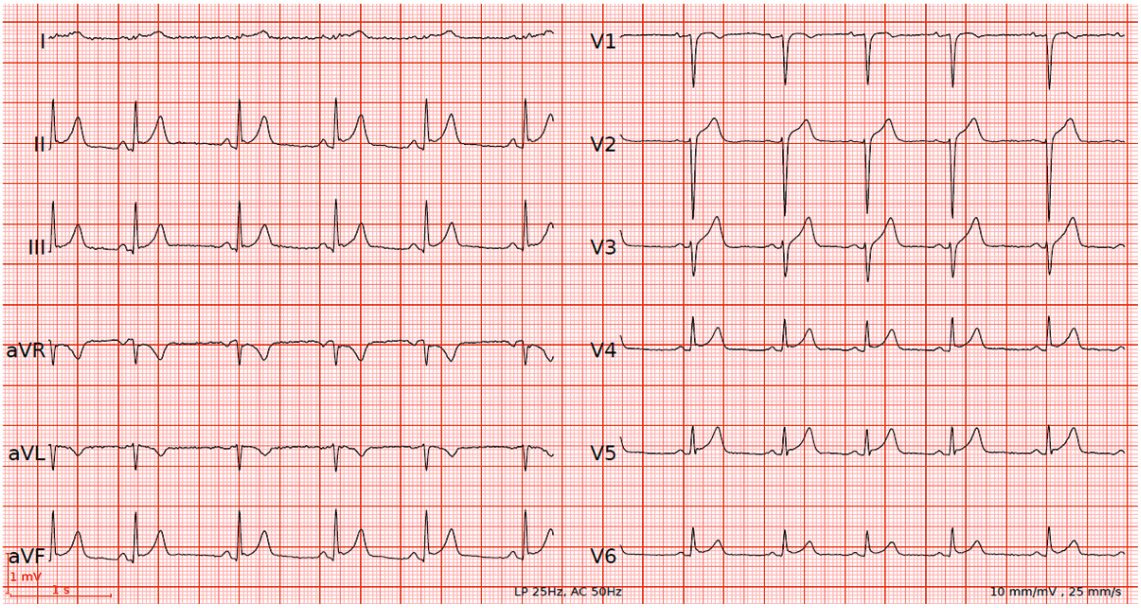
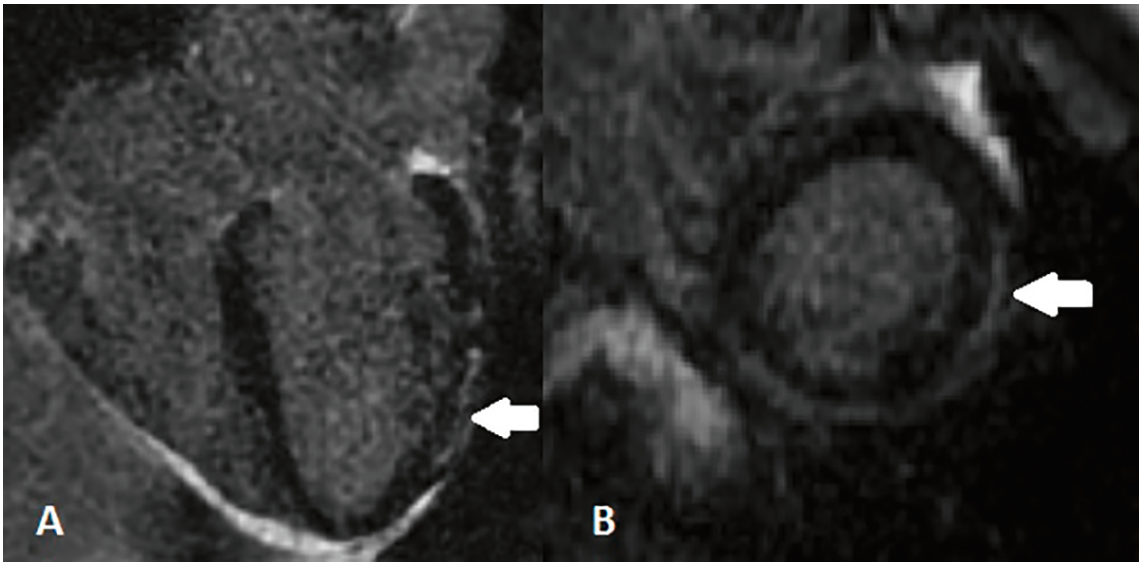


Figure 4: : Patient 2: Cardiac magnetic resonance imaging four chamber view (A) and short axis view (B) showing subepicardial late gadolinium enhancement in the mid to apical lateral and inferior walls (white arrows).



mechanisms are: an immune response to mRNA, molecular mimicry between the spike protein of SARS-CoV-2 and autoantigens, unbalanced cytokine expression and dysregulated triggering of the immunological cascade in genetically predisposed individuals. Sex hormone differences in immune response may, in part, explain the male predominance of vaccine-related myocarditis. Interestingly, myocarditis is more frequent in young males following the second dose, and pericarditis is more frequent in the elderly following the first dose, the reasons for which are unclear [10].

Triage of patients presenting with acute chest pain is of utmost importance. Although, to our knowledge, no cases of acute myocardial infarction related to mRNA vaccination have been reported, STE-ACS suspicion must be high in patients presenting with acute chest pain and ST-segment

Figure 5: : Patient 3: Initial 12-lead ECG showing a sinus rhythm at 91 bpm with diffuse concave ST-segment elevation, and PR segment depression.

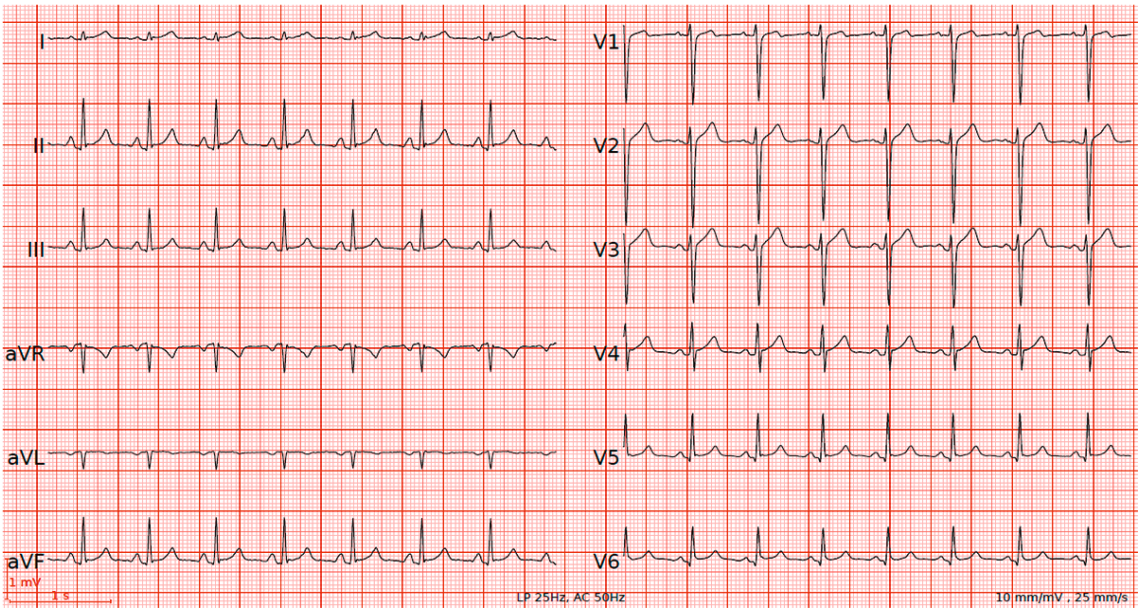


Figure 6: : Patient 3: Cardiac magnetic imaging four chamber view (A) and short axis view (B) showing lateral wall subepicardial late gadolinium enhancement (white arrows).

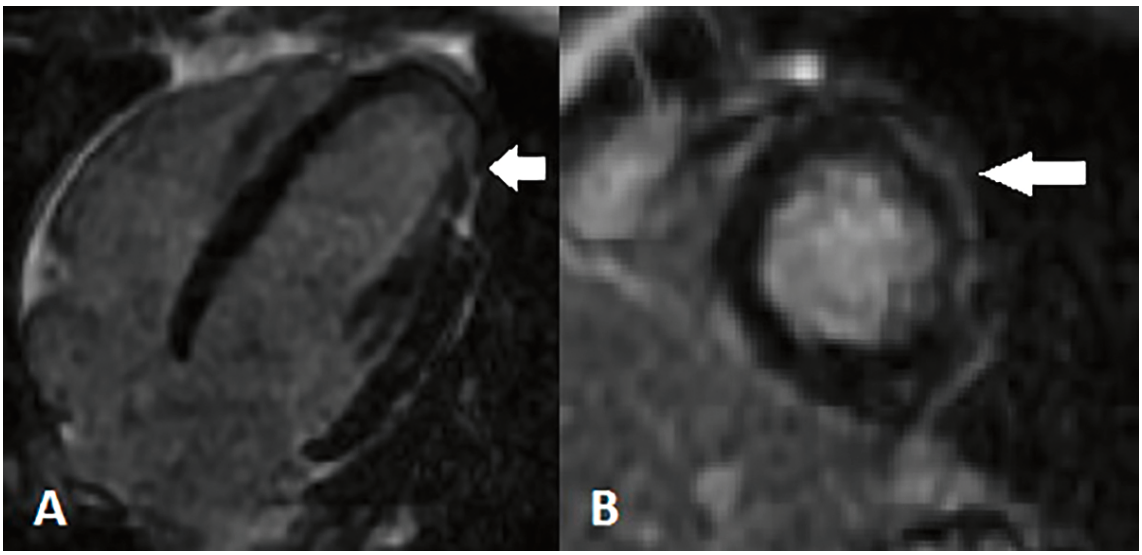


Table 1: :
Age and gender distribution of cases of myocarditis associated with SARS-CoV-2 mRNA vaccine (adapted from reference [7]).

Male 12–29 years old	40.6 cases /1'000'000 second dose
12–17 years old	62.8 cases /1'000'000 second dose
18–24 years old	50.4 cases /1'000'000 second dose
Male >30 years old	2.4 cases /1'000'000 second dose
Female 12–29 years old	4.2 cases /1'000'000 second dose
Females >30 years old	1 case /1'000'000 second dose

elevation on ECG. We present an algorithm for the management of acute chest pain following vaccination against SARS-CoV-2 (fig. 7).

CMR is the current gold-standard for the diagnosis of acute myocarditis [11]. Current guidelines do not recommend extensive aetiological work-up or endomyocardial biopsy in non-severe/fulminant myocarditis responding to appropriate treatment [12].

There are no data for specific management of patients with mRNA vaccine-related myocarditis, and therapy should thus follow general recommendations [13]. Patients may be further stratified into three different risk categories (table 2). Accordingly, therapy ranges from symptomatic treatment to oral heart failure medication, intravenous haemodynamic support, and finally advanced mechanical support. All three of our patients were considered "low-risk" and started on an ACEi. Beta-blockers were avoided in two of them due to sinus bradycardia. There is no clear consensus on treatment duration in the setting of preserved LVEF. We proposed ACEi therapy for 6 months, with a follow-up CMR at that point. Treatment should then be tailored according to the findings (LVEF, LGE) and patient's symptoms. No follow-up of cardiac biomarkers is recommended.

Of note, non-steroidal anti-inflammatory drugs, steroids, and colchicine have been used in patients with mRNA vaccine-associated myocarditis, even though their use in other types of myocarditis is controversial [8]. As of today, no cases of fulminant myocarditis due to mRNA vaccination have been reported.

The incidence of mRNA vaccine-related myocarditis is extremely low, and the benefit of broad vaccination pro-

Figure 7: : Algorithm for acute chest pain following SARS-CoV-2 vaccination. ACS: acute coronary syndrome; CMR: cardiac magnetic resonance; CRP: C-reactive protein; CT: computed tomography; CvRF: cardiovascular risk factors; STE: ST-segment elevation; TTE: transthoracic echocardiography.

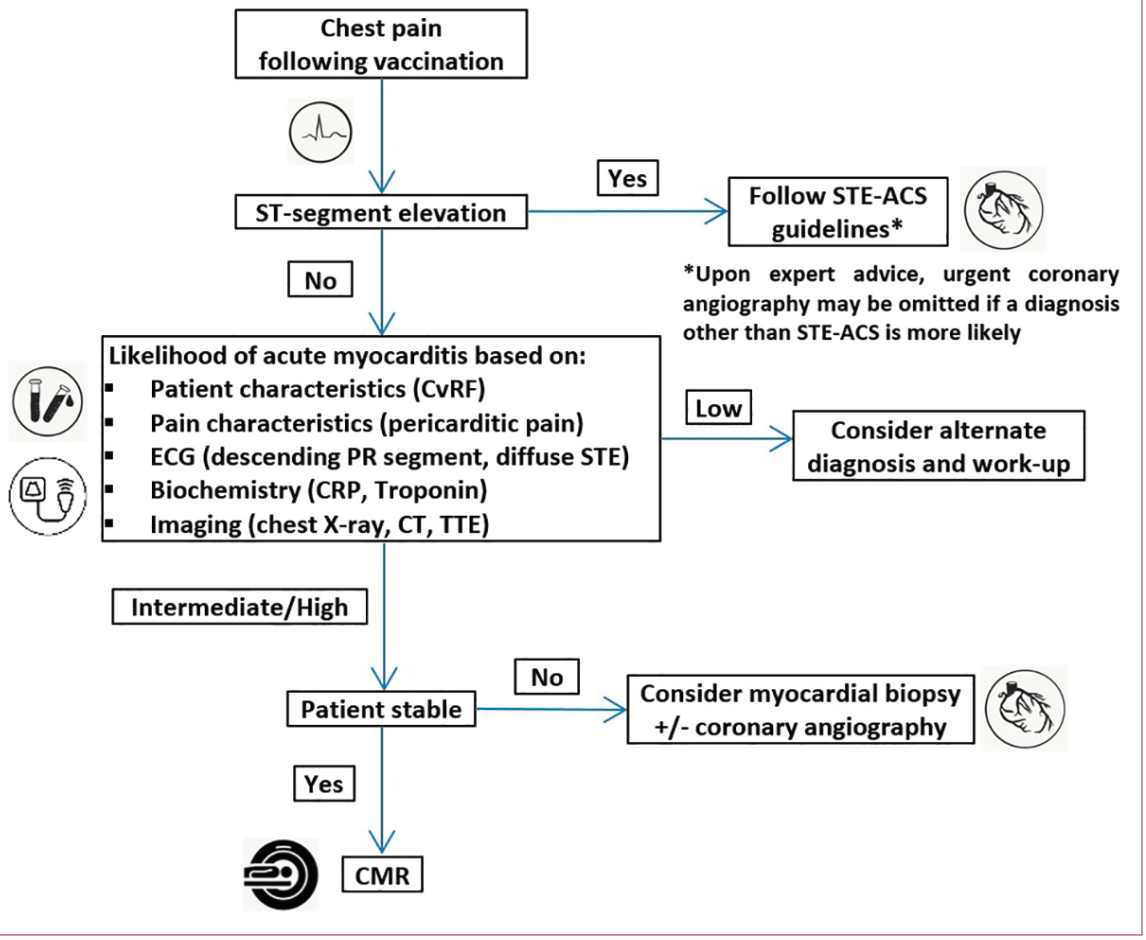


Table 2: :
Risk categories for myocarditis (adapted from reference [13]).

–	"Low-risk": absence of clinical HF or low BP, preserved LVEF (>50%) and absence of arrhythmias.	
–	"Intermediate-risk":	
	a.	Mild HF signs/symptoms, mildly decreased LVEF (41–49%) and presence of arrhythmias.
	b.	HF symptoms, moderately decreased LVEF (30–40%) and absence of arrhythmias.
–	"High-risk":	
	a.	HF symptoms, moderately decreased LVEF (30–40%) and presence of arrhythmias.
	b.	Cardiogenic shock, severely reduced LVEF (<30%) with or without arrhythmias.

BP: blood pressure; HF: heart failure; LVEF: left ventricular ejection fraction

grammes clearly outweighs potential rare side-effects [14]. There is no definitive position on the need for a third vaccine dose. Although there are no data supporting or disapproving it in patients with vaccine-related myocarditis, it would seem wise to refrain from additional doses in this subset of patients until further evidence is published. A third dose with a non-mRNA vaccine could be an alternative. Currently, anaphylaxis to a vaccine compound is the only absolute contraindication [15].

Conclusion

mRNA vaccine-associated myocarditis is increasingly reported in the setting of global vaccination programmes against SARS-CoV-2. Only mild cases of myocarditis have been described, and the benefit of vaccination outweighs rare side effects. With the goal of vaccinating every eligible woman and man, and recent authorisation of the Moderna vaccine for 12- to 17-year-olds in Switzerland, the number of new cases is likely to increase.

Disclosure statement
No financial support and no other potential conflict of interest relevant to this article was reported.

Patient consent
The patients have provided signed consent for the publication of the present case series. A completed patient consent form is available upon request.

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