Acute cardiac side effects after COVID-19 mRNA vaccination, a case series

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Abstract

Background: Since development and approval of the world's first mRNA vaccines, created under pressure of the global pandemic caused by SARS-CoV-2, potential side effects have naturally been a much-debated topic. Vaccination may be one, if not the only way out of the pandemic claiming more than 4 million deaths worldwide to date. Potential side effects from vaccination have long been controversial, and case reports of fatal side effects have been published. Therefore, data are needed to identify persons being at high risk for potential side effects. Until September 30, 2021, 1.243 cases of myocarditis after vaccination with BNT162b2 Comirnaty® in young adults were registered by the Paul-Ehrlich-Institute in Germany alone. The exact pathophysiology and the risk factors for myocarditis following vaccination remain unclear. We present a case series of eight patients with cardiac symptom shortly after SARS-CoV-2 mRNA vaccination (BNT162b6, Biontech, Comirnaty® or mRNA-1273 Moderna, Spikevax®).

Patients and Methods: Eight patients between 13-56 years of age, vaccinated with mRNA vaccine either BNT162b2 or mRNA-1273 between January and August 2021 developed cardiac side effects shortly after either their first or second vaccination. Clinical data were retrieved from the clinical information system and analyzed. To support diagnosis of myocarditis or pericarditis, cardiac magnetic resonance imaging (MRI) was performed shortly after onset of symptoms and investigated further in severe cases. Symptoms were defined as dyspnea, chest pain, cardiac arrhythmia as determined by electrocardiography.

Results: Eight patients (five males and three females) developed cardiac symptoms compatible with myocarditis according to CDC criteria shortly after SARS-CoV-2 mRNA vaccination. Three patients (two males, one female) required hospitalization due to severe chest pain and elevated troponin levels. All patients recovered fully within seven days after symptom onset

Conclusion: Our data suggest that cardiac adverse events such as myocarditis or pericarditis shortly after SARS-CoV-2 mRNA vaccination are rare but possible and occur particularly in male patients.

Introduction

Since the new coronavirus SARS-CoV-2 was identified and is now responsible for a large number of deaths worldwide, there has been no real breakthrough in treatment so far. In medical and public media, the focus is on vaccination rather than medical treatment.

Vaccination is one of the most effective ways to combat the pandemic. The first mRNA-based vaccines targeting SARS-CoV-2 were developed by Biontech Pfizer (BNT162b2, Comirnaty®) and Moderna (mRNA-1273, Spikevax®), investigated by large prospective randomized trials and made obtainable to the world at an extraordinary speed. In studies, mRNA-based vaccination significantly reduced the rate of infection and transmission of SARS-CoV-2, resulting in fewer hospitalizations and deaths^{1,2,3 4} After gaining approval, a worldwide vaccination campaign started at the end of 2020. In this context, of course, the

debate about severe side effects of vaccinations in general has flared up, which has been an ongoing issue for decades. Due to the high number of vaccinations administered in a short period, complications apparently occurred more frequently. In addition, adverse events due to vaccination are currently receiving a very unusual amount of attention. In many of the cases presented in the media, the symptom or disease that occurred is not necessarily due to the vaccination at all.

Therefore, good documentation and interpretation of vaccination side effects is of unspeakable importance to convince the public of the safety of vaccination. Widespread vaccination is the best, if not the only, way to overcome the pandemic.

Myocarditis is a disease often difficult to diagnose, which is based on diagnostic criterias (Fig. 1). Valid data on the incidence of myocarditis are difficult to establish because the gold standard for diagnosis is endomyocardial biopsy, which is not performed regularly^{5,6}. The incidence is approximately 10 to 20 per 100,000 population⁷. Nevertheless, it is a cause of sudden cardiac death in young patients up to 10%, shown in autopsy-based series⁸. Myocarditis is often triggered by viral infections or caused by post-viral immune-mediated responses and up to 30% can progress into a dilatative cardiomyopathy⁹.

Post-vaccination myocarditis has been reported first in 1957 by Dalgaard et al. after vaccination against smallpox¹⁰. Now it is described as a serious complication following mRNA-based vaccines with BNT162b2 or mRNA-1273, most common affecting young healthy adults¹¹⁻³⁴. This is particularly important since this subgroup of individuals is not at high risk for a severe COVID-19 disease course if symptomatically infected. Since the two vaccines are substantially different, further studies on the pathophysiology are of high interest.

Here, we report a case series of eight consecutive patients with cardiac side effects after inoculation of either the first or the second dose of a mRNA vaccine.

Patients, Material And Methods

Retrospective analysis of eight consecutive patients (5 male, 3 female), from 15 to 56 age of years, who presented in hospital with symptoms compatible with myo- or pericarditis shortly after first or second SARS-CoV-2-mRNA-vaccination. Vaccination was performed by either BNT162b6 or mRNA-1273 and in the recommended time intervals. We used the Centers of Disease Control and Prevention (CDC) diagnostic criteria to interpret symptoms and determine the diagnosis of myocarditis or pericarditis, presented in Figure 1. Medical history and further diagnostic, e.g. coronary catheterization, did not reveal any alternative causes. The data were collected in our patient database and were sampled routinely. We examined the reports on cardiac side effects from the Departments of Infections Disease at the University of Dusseldorf, Department of Pediatrics University of Dusseldorf, Department of Cardiology University of Dusseldorf, Department of Cardiology and Rhythmology, Petrus Hospital, Wuppertal, Department for Cardiology, Rhythmology, Angiology and Intensive Care Medicine EVK Dusseldorf and reports from the Division of Experimental Anesthesiology from the University Hospital Ulm.

The study retrospectively analysis of data was approved by the local ethics committee of the Heinrich-Heine University Düsseldorf (Study-Number: 2021-1698).

The following scheme reveals the diagnostic criteria (based on the CDC) that were used as a basis for grading symptoms¹¹.

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Coronavirus disease 2019 (COVID-19) vaccines. Accessed July 6, 2021.
<https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html>

Results

Specific patient data are described below. A summary of their data is provided in Table 1.

Patient 1:

A 13-year-old healthy Caucasian male presented with chest pain two days after his second dose of SARS-CoV-2 mRNA-vaccine BNT162b2, Comirnaty[®]. No other symptoms were present. Troponin I level was elevated up to 150 ng/ml (normal level < 14 ng/ml) at the day of presentation and increased to 307 ng/ml on day 3 after admission. N-terminal fragment of the BNP precursor (NT-proBNP) was elevated to 520 pg/ml (normal level 10-157 pg/ml) on day 3. Further virological and microbiological examination revealed positive IgM-antibodies against mycobacterium pneumoniae IgM EIA 0.97 (normal level < 0.80). Antibodies titer against other cardiotropic infective agents like toxoplasma gondii or borellia burgdorferi were negative. Since an infectious myocarditis caused by M. pneumoniae could not be ruled out, therapy with azithromycin for 4 days was initiated. A cardiac MRI was performed at day 2 and signs of a mild myocarditis with edema were detected. The troponin I decreased rapidly into the physiological range within 5 days. After one week in the intermediate care unit, the patient could be discharged home fully recovered.

Patient 2

A 28-year-old healthy Caucasian male presented with dyspnea and left sided chest pain 3 days after the second dose of the mRNA- vaccine BNT162b2, Comirnaty[®]. A few hours after the second dose, the athletic patient developed increasing shortness of breath at the lowest exercise level with pectanginous complaints. Nevertheless, on day 3 after vaccination he started exercising but went to our outpatient clinic. Four days after the second dose, the symptoms were persisting, but troponin I and NT-proBNP were not elevated. C-reactive protein and white blood cell count were also within normal limits. Electrocardiogram showed transient mild but significant ST-Elevations and widening of the QRS complex in the limb leads. Six days after the second vaccination dose, the transient ST alterations disappeared but a mild preterminal T-negativity in lead III persisted. NT-proBNP and Troponin I remained within normal limits with 4 ng/l (normal level <14 ng/l). It was higher on day 4, but still in the normal range. Transthoracic echocardiography was performed on day 6 after vaccination, revealing globally and

regionally normal left ventricular function, a normal right ventricular function, normal cavities and wall thicknesses, no signs of valvular dysfunction and no pericardial effusion. No cardiac catheter or cardiac magnetic resonance imaging was performed. The patient did not develop uncontrolled high blood pressure. The symptoms fully resolved within 7 days.

Patient 3

A 28-year-old male presented two days after the second dose vaccination with mRNA1273, Spikevax® with acute chest pain and ST-elevation mimicking ST elevation myocardial infarction (STEMI) in the emergency Department. Due to a history of type-1-diabetes, an immediate cardiac catheterization was performed, ruling out obstructive coronary artery disease (CAD). Initial Troponin-T was 755 pg/ml (normal value < 14 pg /ml), rising to 894 pg/ml the next day; creatine kinase was 657U/l, CK-MB 49U/l, falling to 533 and 39U/l respectively. C-reactive protein was 4.0 mg/dl (normal value 0.8-1 mg/dl), decreasing to normal levels on day 3. Initial echocardiography revealed slightly impaired left ventricular function; CMR after 3 days showed a normalization of the left ventricular function and epimyocardial late enhancement.

One week holter monitor showed no rhythm abnormalities. After one week, CK and Troponin were within normal range and the patient did not complain about chest pain. The patient was discharged on day 7 fully recovered.

Patient 4

A 56-year-old female with a congenital metabolic disorder (lipoproteinemia) presented two days after her second dose with mRNA1273 Spikevax® with shortness of breath, sinus tachycardia with up to 100 beats per minute and chest pain. An ECG showed an inverted t-wave most prominent in the lateral leads. After one week, symptoms and t-wave inversion disappeared but the patient still suffered from a mild fatigue. No cardiac catheter or magnetic resonance imaging or echocardiography were performed.

Patient 5

A 42-year-old athletic male developed two days after his second dose with Comirnaty®, for the first time shortness of breath and sinus tachycardia with 110 beats per minute. There were neither history of cardiac disease nor high blood pressure. An ECG revealed inverted t-waves in the lateral leads. No elevated blood pressure occurred. Climbing steps was difficult for several days. After one week, the cardiac symptoms disappeared. No cardiac catheter or magnetic resonance imaging or echocardiography was performed.

Patient 6:

A 42-year-old male presented at the emergency department of a teaching hospital of the University of Düsseldorf with a singular incident of acute chest pain 10 days after the second vaccination with Spikevax®. Immediately after vaccination he experienced fever and illness for a few days. Initial

Troponin-T was 286pg/ml (normal value <14 pg/ml), falling to 92pg/ml after 3 days at discharge. Creatine kinase was normal at admission and during the hospital stay. Coronary angiography excluded obstructive CAD, MRI showed late enhancement indicating myocarditis (epicardial enhancement, predominantly at the lateral LV).

Patient 7:

A 29-year-old female presented at the emergency department with intermittent chest pain 1 day after the first vaccination with BNT126b. Initial Troponin-T was 414pg/ml (normal value <14 pg/ml), rising up to 440pg/ml, falling to 56pg/ml after 4 days. Creatine kinase was 484U/l and normal at discharge after 5 days. MRI showed signs of myocarditis (epicardial enhancement of the posterolateral LV wall).

Patient 8:

A 15-year old Caucasian female patient with a known limb girdle muscle dystrophy type 2d presented with chest pain 3 days after the second dose of SARS-CoV-2 mRNA-vaccine Comirnaty®. The day after vaccination, she developed fever up to 39°C, reporting similar symptoms after the first dose. Due to progressive chest pain, she was admitted to the pediatric ward. Troponin T levels were elevated up to 1438 ng/ml at admission, while NT-proBNP was elevated to 300 pg/ml (normal level 6-158 pg/ml). Both Troponin T and NT-proBNP decreased rapidly during the following days and reached nearly normal levels at discharge (Troponin T 81 ng/ml, NT-proBNP 62 pg/ml).

Due to the known muscular dystrophy, cardiac enzymes were differentiated into Troponin I (264 ng/ml, norm: < 17,5 ng/ml) and Troponin T (136 pg/ml, norm <14 pg/ml).

A cardiac magnetic resonance imaging (CMR) was performed on day 4 revealing signs of a mild myocarditis with edema and elevated T2-relaxation-times. Initially echocardiography was performed and showed decreased strain function which normalized within the next two days.

Further virological and microbiological examination did not reveal any indications for an infectious myocarditis.

After 5 days in the intermediate care unit, the patient could be discharged without any clinical residues.

Discussion

We are presenting a consecutive series of eight patients, age 13 to 56 years, presenting with symptoms compatible with acute myocarditis or pericarditis after the first or mainly second vaccination with either BNT126b2 or mRNA-1273 against SARS-CoV-2. Prevalent symptoms were dyspnea or chest pain. All patients recovered rapidly without residuals, though lacking long-term follow-up.

Myocarditis has been a rare post-vaccination event, recently typically observed several days after mRNA-based COVID-19 vaccines like BNT126b2 or mRNA-1273. Symptoms and their onset, mean of 1-5 days

post vaccination, were similar to the data presented by Diaz et al in JAMA³⁵, Das et al. in Children¹² and Jain et al in Pediatrics.²⁷

The pathophysiology still remains unclear. Definite diagnosis of a myocarditis or pericarditis and demonstration of causal relationship to the vaccination is challenging. The CDC defined symptoms and signs for a probable or confirmed myocarditis or pericarditis including chest pain, shortness of breath, feelings of having a fast beating, fluttering or pounding heart. Diagnostic work-up at the emergency department includes ECG, Troponin, CK/CK-MB, CRP and echocardiography.

Myocardial biopsy is considered as gold standard, but is not routinely performed due to its invasiveness.

In Patient 1, the 13-year-old male presented with chest pain having a positive detection of M pneumoniae-IgM, the titer was IgM EIA 0.97 (normal level < 0.80). Because M pneumoniae can cause chest pain, further examination was necessary, but sensitivity of one serological test at the time of symptom onset is very low with about 31.1%. It increases after a second test up to 86% (Ozaki et al.)²⁷. No other symptoms compatible with a respiratory infection caused by M. pneumoniae were present, but myocarditis triggered by mycoplasma are possible. However, M. pneumoniae-IgM can persist up to one year after an infection. In this case, considering the mentioned facts, we assume that myocarditis was not caused by M. pneumoniae and was more likely triggered by the vaccination with BNT162b2. Patient 1 meets therefore all criteria for a confirmed myocarditis with dyspnea, chest pain, elevated Troponin and NT-proBNP, edema in CMR and no other reasonable explanation could be detected.

In Patient 2, we had a young healthy male with no history of cardiovascular disease or clinic signs like angina pectoris, dyspnea or palpitations and the symptoms occurred in the typical time frame after the SARS-CoV-2 vaccination. In Patient 3, an immediate cardiac catheterization was performed, ruling out coronary heart disease. Thus, these reactions after the mRNA vaccination are consistent with the recently published literature, reporting similar reactions after the administration of BNT162b2 approved vaccinations

In patients 2, 4 and 5, shortness of breath, sinus tachycardia up to 110 beats per minute with palpitations were the leading symptoms after the second dose with mRNA vaccination against SARS-CoV-2. In Patient 5, ECG abnormalities were seen. In all these patients, symptoms disappeared within one week.

Patient 1 is a well-documented case of perimyocarditis with complete resolution with no recognizable clinical long-term effects in a young male patient who falls into the well-known spectrum of this rare side effect. The other cases are more or less likely the same acute cardiac side effects of a SARS-CoV-2 vaccination against the Spike protein.

Patients 6 and 7 are well documented with elevated heart enzymes and confirmed myocarditis in both cases.

Patient 8 reports a 15-year old female patient with progressing chest pain. Due to her pre-existing condition, myocarditis wasn't the initial diagnosis and no CMR was performed immediately. With missing progressing symptoms of her known muscular dystrophy and known elevated heart enzymes, vaccination-associated myocarditis was more likely than any condition related to the muscular dystrophy. However, her pre-existing condition cannot be ruled out for these symptoms and reaction.

These are - very often mild - cases in younger males and patients tend to recover within a short time after standard treatment and rest. Healthcare professionals should know this side effect and should be cautious if these signs and symptoms occur. In literature, the reported incidence is 1:20.000 for myocarditis and pericarditis after the second dose in younger men. The phenomenon is transient and typically resolves within 3-5 days, frequently without any treatment required. Patients should preferably avoid physical exertion for several weeks, but data supporting this is rare.

Our data, despite the small patient population, seems to be consistent with earlier reports documenting the relative short time from the second dose administration and the development of myocarditis. Vaccinated people should also try to find instant medical attention when experiencing new onset of chest pain, shortness of breath, palpitations or arrhythmias. Nevertheless, since myocarditis of any cause can have medical implications for the patients further life, regular cardiological check-ups are suggested.

Conclusion

Cardiac side effects like myocarditis are a rare side effect that can present as a localized, transient event several days after the first or second dose of the mRNA-based COVID-19 vaccines. Vaccinated should be notified that a myocarditis could occur especially in young males. Further investigations on the precise molecular and cellular mechanisms underlying this side effect are needed to understand why and when rare adverse events may occur after S protein encoding vaccines. Close clinical follow-up of confirmed cases should be performed. Affected patients should consider close cardiological checks.

Abbreviations

CDC: Center for Disease control and Prevention

COVID-19: coronavirus disease 2019,

CK: creatine kinase

CRP: C-reactive protein

DNA: deoxyribonucleic acid

IgM: immunoglobulin M

mRNA: messenger ribonucleic acid

SARS-CoV-2: severe acute respiratory syndrome coronavirus-2

MRI: magnetic resonance imaging

NT-proBNP: N-terminal probrainnatriuretic peptide

STEMI: ST-segment elevation myocardial infarction

CK: creatine kinase

CK-MB: creatine kinase M: myocardial, B: brain

Declarations

Authors' contribution

NFF, EB, OG, MP, JN, DJ, TF, MS, HS, AR and CM wrote parts of the manuscript. EB; MP, NF; OG and CM did the literature research and prepared the data for analysis. All authors read the manuscript. NF, EB, MP, CM contributed significantly to the discussion on the interpretation of the results. All authors read and approved the final manuscript. EB, CM and MvG are editors of the journal.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

All data and materials can be accessed via CM and MK.

Consent for publication

All authors gave consent for the publication

Ethics approval and consent to participate

This retrospective study was approved by the local ethical commission.

Conflict of Interest: All authors declare that they have no conflict of interest.

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Table

Table 1 – Case description of the 8 patients who developed cardiac side effects after vaccination against SARS-CoV-2.

Case	Age (years)	Sex	Vaccine	Comorbidity	First / second injection	Time onset of the cardiac reaction (days)	Treatment	Relief of symptoms (days)
1	13	Male	Comirnaty®, BNT126b2	No	Second	3	Observation, intermediate care	5
2	28	Male	Comirnaty®, BNT126b2	No	Second	2	Observation	7
3	28	Male	Spikevax®, mRNA-1273	Diabetes mellitus Typ 1	First	2	Observation Intermediate care	3
4	56	Female	Spikevax®, mRNA-1273	Metabolic syndrome	Second	2	Observation	7
5	42	Male	Comirnaty®, BNT126b2	No	Second	2	Observation	7
6	42	Male	Spikevax®, mRNA-1273	No	Second	10	Observation Intermediate care	3
7	29	Female	Comirnaty®, BNT126b2	No	First	1	Observation Intermediate care	5
8	15	Female	Comirnaty®, BNT126b2	girdle muscle dystrophy type 2d	Second	3	Hospitalization	5

Figures

Diagnostic Criteria for myocarditis and pericarditis following the CDC

Acute Myocarditis

Probable Case.

Existence of ≥ 1 new or worsening of the following symptoms
Chest pain / pressure/ discomfort
Dyspnoe/ shortness of breath
Palpitations / syncope
And ≥ 1 new findings of elevated troponin above upper limit of normal
Abnormal ECG or rhythm monitoring finding consisting with myocarditis
Abnormal cardiac function or wall motion abnormalities on echocardiogram
Cardiac MRI findings consistent with myocarditis
And no other identifiable cause of the symptoms and findings

Confirmed Case

Presence of 1 or more new worsening of the following symptoms
Chest pain / pressure / discomfort
Chest pain / pressure/ discomfort
Dyspnoe/ shortness of breath
Palpitations / syncope
And
Histopathologic confirmation of myocarditis
Or
Elevated troponin levels above upper limit of normal and cardiac MRI findings consistent with myocarditis
And
No other identifiable cause of the symptoms and findings

Acute pericarditis

Presence of ≥ 2 new or worsening of the following clinical symptoms

Acute chest pain (typically described as pain made worse by lying down, deep inspiration, cough and relieved by sitting up or leaning forward, although other types of chest pain may occur)

Pericarditis rub on exam

New ST elevation or PR depression on ECG

New or worsening pericardial effusion on echocardiogram or MRI

Autopsy cases may be classified as pericarditis on basis of meeting histopathologic criteria of the pericardium

The following scheme shows the diagnostic criteria (based on the CDC) that we used as a basis for grading symptoms¹¹.

Centers for Disease Control and Prevention (CDC). Advisory Committee on Immunization Practices (ACIP). Coronavirus disease 2019 (COVID-19) vaccines. Accessed July 6, 2021. <https://www.cdc.gov/vaccines/acip/meetings/slides-2021-06.html>

Figure 1

See image above for figure legend.

Figure 2

ECG performed on day 4 (A) and on day 6 (B) after the SARS-CoV-2 vaccination in a 28-year-old male. A: Widening of the QRS complex (112ms) in all ECG leads, and ST-Elevations in I, II, III, , aVF and inverted in

aVR. **B:** The transient widening of the QRS complex has receded. There is left only a mild preterminal T negativity in lead III.

Figure 3

Cardiac magnetic resonance imaging (CMR): showed epicardial late enhancement apical lateral suggestive of myocarditis

Figure 4

Cardiac magnetic resonance imaging (CMR): showed myocarditis (epicardial enhancement, predominantly at the lateral LV).

Figure 5

Cardiac magnetic resonance imaging (CMR): showed myocarditis (epicardial enhancement of the posterolateral LV wall).

Cardiac Symptoms after vaccination against SARS-CoV-2

Figure 6

Flowsheet for diagnostic work up once cardiac events occurred after Sars-CoV-2 vaccination.