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COVID-19 vaccine-associated myocarditis in an adolescent after the third vaccine dose. Case report with follow-up

Zapalenie mięśnia sercowego po zastosowaniu trzeciej dawki szczepionki przeciwko COVID-19 u nastolatka. Analiza przypadku i dalsza obserwacja

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Abstract

We report on the case of a 16-year-old boy with myocarditis developing after the third dose of COVID-19 mRNA vaccine. The patient presented with fever and retrosternal chest pain two days after immunisation. On admission, the boy was in good condition, with stable vitals. Elevated serum troponins and electrocardiographic repolarisation abnormalities with normal echocardiographic contractility were noted. Cardiac magnetic resonance imaging revealed active myocarditis in form of oedema with late gadolinium enhancement in five segments of the left ventricle myocardium. During further hospitalisation, rapid improvement in the patient's general condition with normalisation of troponin level, and regression of electrocardiographic abnormalities were observed. In follow-up reassessments at three and nine months, cardiac magnetic resonance revealed residual myocardial lesions. No symptoms and abnormalities in laboratory tests, electrocardiography, or echocardiography were found. It is imperative to exercise full vigilance for COVID-19 vaccine-associated myocarditis when chest pain appears following vaccination, even in the absence of alarming symptoms after previous vaccine doses.

Keywords: myocarditis, vaccination, COVID-19, children

Streszczenie

W pracy przedstawiono przypadek nastolatka z zapaleniem mięśnia sercowego po otrzymaniu trzeciej dawki szczepionki mRNA przeciwko COVID-19. Chłopiec zgłosił się do szpitala z powodu gorączki i zamostkowego bólu w klatce piersiowej, które wystąpiły 2 dni po szczepieniu. Przy przyjęciu stan chorego był dobry, parametry życiowe – w normie. Stwierdzono wzrost stężenia troponiny i zaburzenia repolaryzacji w badaniu elektrokardiograficznym, bez zaburzeń kurczliwości w badaniu echokardiograficznym. Rezonans magnetyczny serca ujawnił cechy aktywnego stanu zapalnego pod postacią obrzęku z towarzyszącymi obszarami późnego wzmocnienia pokontrastowego w pięciu segmentach mięśnia lewej komory. Podczas hospitalizacji obserwowano poprawę stanu ogólnego, normalizację stężenia troponiny i regresję nieprawidłowości w badaniu elektrokardiograficznym. W ramach badań kontrolnych po 3 i 9 miesiącach w badaniu rezonansu magnetycznego serca opisywano zejściowe zmiany pozapalne. Nie obserwowano niepokojących objawów ani nieprawidłowości w pozostałych badaniach dodatkowych. W przypadku bólu w klatce piersiowej po szczepieniu przeciwko COVID-19 zawsze należy wykluczyć zapalenie mięśnia sercowego, nawet jeśli po poprzednich dawkach nie notowano niepokojących objawów.

Słowa kluczowe: zapalenie mięśnia sercowego, szczepienie, COVID-19, dzieci

INTRODUCTION

Vaccines against the coronavirus disease 2019 (COVID-19) contributed to a prominent global decline of COVID-19-related morbidity and mortality, also in the paediatric population[1]. According to the Centers for Disease Control and Prevention (CDC) guidelines for the paediatric population, COVID-19 vaccination is recommended for all children from the age of six months, if eligible. In rare cases, serious side effects, including COVID-19 vaccine-associated myocarditis (C-VAM), may occur[2]. To date, the most frequently reported C-VAM cases involve young males, most commonly after the second vaccine dose[3]. Over the last few months, there have been isolated reports of C-VAM after the third dose of COVID-19 vaccination in the adult population[4]. To our best knowledge, up to now, only two full descriptions of the course of COVID-19 third-dose-related isolated C-VAM and one case report of myocarditis with concomitant pericarditis have been published among the paediatric population[5,6]. We present the first case study of an adolescent with C-VAM developing after the third vaccine dose. It is worth emphasising that this is the first case report with further follow-up including cardiac magnetic resonance imaging (MRI) at three and nine months after diagnosis.

CASE REPORT

A 16-year-old male patient presented to the emergency department with recurrent fever of up to 38.9°C for two days, accompanied by shivering and crushing, periodically diminishing, retrosternal chest pain. The patient had been vaccinated against COVID-19 with a third dose of BNT162b2 two days before hospital admission. There was no history of any previous infections within the last month, including COVID-19, and no adverse effects after the first and second doses of the COVID-19 vaccine.

On admission, the boy was in good condition, with stable vitals. Physical examination revealed muffled heart sounds without tachycardia or signs of heart failure. A blood test panel revealed significantly increased troponin I (31,447.3 ng/L, normal <19 ng/L), moderately raised N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (692 pg/mL, normal <125 pg/mL), and C-reactive protein (CRP) (6.65 mg/dL, normal <0.5 mg/dL) levels (Tab. 1). On electrocardiogram (ECG), ST segment elevation in the I, II, aVL, and V4–V6 leads, and ST depression in the III, aVR, and V2 leads were noted (Fig. 1 A). Chest X-ray revealed no abnormalities. Transthoracic echocardiography including 3D ventricular function assessment showed normal left ventricle

Laboratory test	
Troponin [ng/L]: • admission • day 3 • day 5 • day 7	 31,447.3 6,692 216.1 18
NT-proBNP [pg/mL] • admission • discharge	 692 54
CRP [mg/dL]: • admission • discharge	 6.65 0.16
Additional tests	
ECG	ST segment elevation in I, II, aVL, V4–V6 leads. ST segment depression in III, aVR and V2 leads
Echocardiography: • % EF • left ventricular end diastolic diameter [mm] • regional wall motion changes and pericardial effusion	 62 48.6 No changes
Cardiac MRI: • myocardial oedema (T2 mapping), segment of left ventricle • subepicardial and intraventricular LGE in segments	 Basal infero-lateral segment Basal, middle infero-lateral and apical lateral segments
Follow-up cardiac MRI	
3 months: • myocardial oedema (T2 mapping), segment of left ventricle • subepicardial and intraventricular LGE in segments	 No changes Basal infero-lateral segment
9 months: • myocardial oedema (T2 mapping), segment of left ventricle • subepicardial and intraventricular LGE in segments	 No changes Basal infero-lateral segment

Cardiac MRI – cardiac magnetic resonance imaging; **CRP** – C-reactive protein; **EF** – ejection fraction; **ECG** – electrocardiography; **LGE** – late gadolinium enhancement; **NT-proBNP** – N-terminal prohormone of brain natriuretic peptide.

Tab. 1. Laboratory and additional tests

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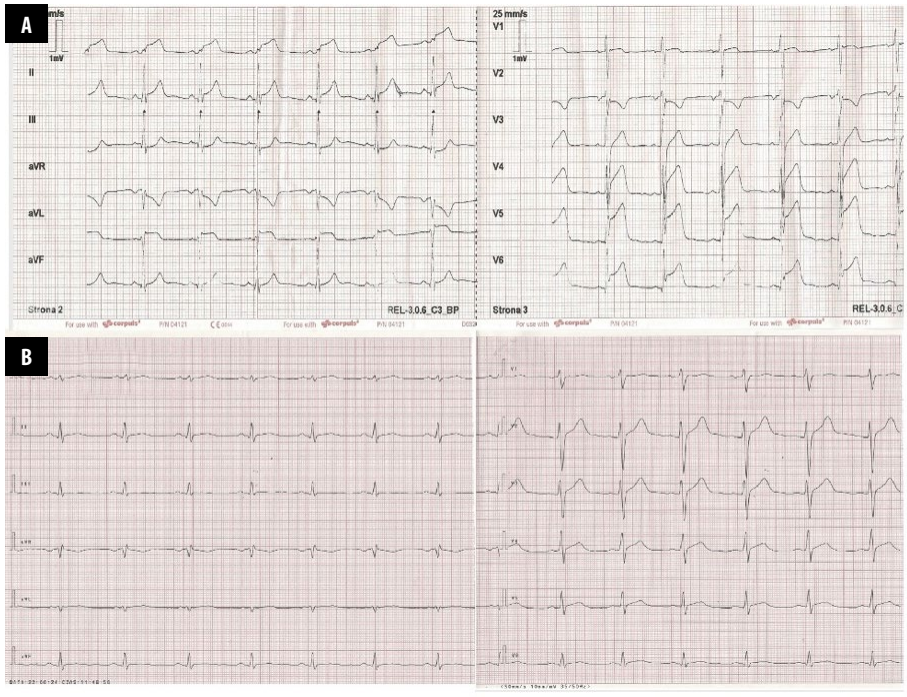

Fig. 1. **A.** *ECG on admission: ST segment elevation in I, II, aVL, V4–V6; ST segment depression in III, aVR, and V2 leads.* **B.** *ECG on day 7 after admission. Resolution of ST elevation and depression. Repolarisation abnormalities in the form of flat T waves in I, II, III, aVL*

size and function. There were no wall motion abnormalities or pericardial effusion. No arrhythmia was detected on Holter ECG monitoring. Based on anamnesis, physical examination, ECG findings, laboratory data, and the temporal correlation between vaccination and symptoms of COVID-19, C-VAM was suspected. Cardiac MRI performed on the second day of hospitalisation (four days after vaccination) confirmed the diagnosis of myocarditis according to the 2018 Lake Louise criteria for myocarditis and CDC criteria for C-VAM[2,7,8]. Cardiac MRI revealed preserved ejection fraction, normal size of the left ventricle, and myocardial oedema in five segments of the left ventricular wall corresponding to the location of areas of mid-subepicardial late gadolinium enhancement (LGE) (Fig. 2 A, 2 B). Serological testing excluded coxsackie virus, parvovirus B19, SARS-CoV-2, HSV1, HSV2, HHV6, HHV7, and enterovirus aetiologies.

Meeting the above criteria obliged us to make a diagnosis of C-VAM, implement appropriate diagnostic and therapeutic procedures, and report the case to the appropriate vaccine adverse reaction monitoring services. All of the above-mentioned measures were immediately applied to our patient.

During further hospital stay, rapid improvement of the patient's general condition with complete symptom resolution within four days from disease onset was observed. ECG evolution, followed by a rapid drop in troponins, were noted (Fig. 1 B). On day 5 of hospitalisation, the patient' troponin level was 216.1 ng/L, with total normalisation on day 7 (Tab. 1). The patient was treated only with oral lisinopril and did not require any other medical interventions.

Three months after hospital discharge, the boy's general condition was reassessed, and additional tests were performed. The patient did not present any of the previously described symptoms, including chest pain. Troponin I and NT-proBNP levels were normal. No abnormalities in the ECG pattern and 24-hour ECG monitoring were observed either. Follow-up cardiac MRI revealed small subepicardial left ventricular LGE areas in the basal-inferolateral segment of different aetiology than ischaemic, without myocardial oedema. The patient's cardiac MRI results did not meet the 2018 myocarditis Lake Louis criteria and reflected decreasing residual myocardial lesions (Tab. 1).

The next follow-up appointment was scheduled at nine months after the first hospitalisation. Similarly to the previous assessment, the patient did not present any symptoms, and there were no abnormalities in laboratory tests, ECG, or echocardiography. Follow-up cardiac MRI, as before, showed minor intramuscular areas of LGE within the same basal-inferolateral myocardial segment (Tab. 1).

DISCUSSION

The safety and efficacy of COVID-19 BNT162b2 mRNA vaccine are well-established also in the paediatric population. Despite the high level of COVID-19 protection, the possibility of mRNA vaccine-induced side effects should always be considered. The most commonly reported symptoms, i.e. pain and redness at the injection site, are mild and transient. Non-specific systemic reactions, such as headache, fatigue, chills, and myalgia, are also relatively widespread. In rare cases, serious reactions in the form of

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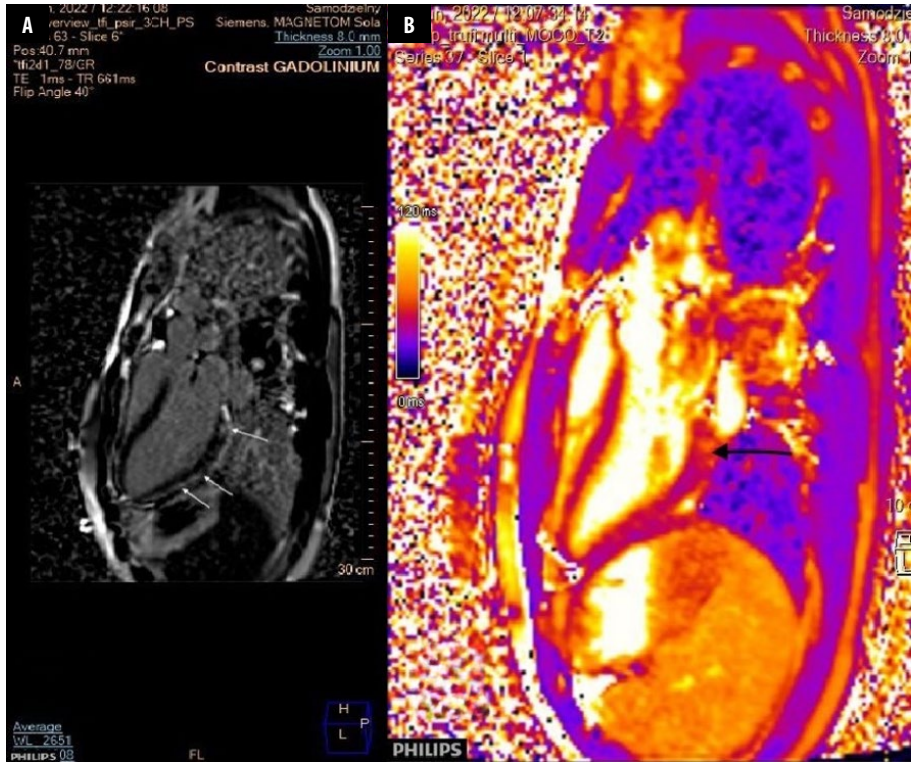

Fig. 2. **A.** *Cardiac MRI of myocarditis after the third dose of COVID-19 vaccine. T2 mapping demonstrates oedema in basal infero-lateral segment (arrows).* **B.** *Phase-sensitive inversion recovery (PSIR) image shows the area of late gadolinium enhancement (LGE) located in the basal, middle infero-lateral, and apical lateral segments of the left ventricle (arrows)*

lymphadenopathy, thrombotic events, anaphylactic shock, and cardiovascular complications may occur[1,2].

It should be noted that myocarditis may also be a complication of other vaccinations used widely in the paediatric population. To date, a temporal relationship between vaccination and symptoms of myocarditis after immunisation against influenza, smallpox, and tetanus has been described[9].

To date, the highest risk of C-VAM has been reported in the adolescent and young adult male population (especially in the range between 16 and 17 years of age). However, in the studies published so far, the highest incidence of C-VAM was related to patients immunised with the second dose of mRNA vaccine[3].

The course of the disease in the reported case was mild, and the patient did not present any serious complications. The onset of chest pain two days after vaccine administration was observed. In addition, typically for myocarditis, significantly increased serum troponin levels and electrocardiogram abnormalities were found. Cardiac MRI revealed myocardial oedema corresponding to areas of late gadolinium enhancement without left ventricle systolic function impairment in echocardiography.

Because of the gradually growing global C-VAM problem, in 2021 the CDC, based on experience gained from varicella zoster vaccine-associated myocarditis, introduced the criteria for confirmed and probable C-VAM. New-onset temporal-associated with vaccine administration symptoms, elevated troponin levels, and cardiac MRI findings consistent with the 2018 Lake Louis criteria for myocarditis are crucial for confirmed C-VAM diagnosis. It is also extremely important to exclude other potential causes of myocarditis, such as viral infections, drug use, medicines, and others[2,7,8]. Since the criteria for a diagnosis of C-VAM were met, all recommended diagnostic and therapeutic procedures were promptly implemented, and the case was reported to the appropriate vaccine adverse reaction monitoring service.

Similarly, to the C-VAM cases following the second vaccine dose, rapid symptom resolution with general condition improvement and quick troponin level normalisation were observed[3].

Despite the lack of any concerning symptoms and normal troponin levels on follow-up reassessments (at three and nine months after diagnosis), LGE lesions were still present on cardiac MRI. However, they did not meet the criteria for active myocarditis. Thus, it seems that, similarly to C-VAM after the second dose, rapid symptom regression with troponin level normalisation does not reflect complete resolution of myocardial injury[10].

Regardless of the significance of the C-VAM problem, it should be mentioned that in the population under 40 years of age (including paediatric patients) the risk of myocarditis due to COVID-19 seems to be significantly higher when compared to the risk of C-VAM. Moreover, it has been proven that vaccinations reduce the risk of myocarditis related to COVID-19 approximately by half[11]. Therefore,

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COVID-19 immunisation may have an additional benefit in the prevention of long-term cardiovascular consequences of COVID-19 also in the paediatric population. In addition, C-VAM is characterised by a statistically lower rate of heart failure, dilated cardiomyopathy disorder, and lower mortality within 180 days of diagnosis, when compared to viral infection-related myocarditis[12].

Recent reports indicate that the highest risk of C-VAM after the third mRNA vaccine dose is seen in the male population in the 16–19 years age range. In addition, the incidence risk of C-VAM developing after the third dose in this group appears to be significantly lower compared to the second dose (6.44 per 100,000 individuals and 14.89 per 100,000, respectively)[13–15].

A group of special interest in the context of COVID-19 vaccination is the population with a history of multisystem inflammatory syndrome in children (paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2, PIMS). Misregulation of the immune response stemming from the disease raises concerns about the risk of myocarditis after COVID-19 immunisation. In accordance with the latest CDC guidelines, to reduce the risk of adverse effects, including C-VAM, it is recommended that vaccination be postponed for at least 90 days after diagnosis[2]. COVID-19 vaccination after the above-mentioned period seems to be safe, and to date there is no strong evidence of an increased risk of C-VAM after PIMS diagnosis when compared to the healthy population[16]. The benefit of COVID-19 vaccination in the form of reducing the risk of PIMS has also been reported in recent literature[17].

According to the latest CDC guidelines, COVID-19 immunisation is recommended for all individuals aged six months and above, including at least one bivalent mRNA updated dose against new COVID-19 mutations. Therefore, the number of people vaccinated against COVID-19, including the third and subsequent doses, is steadily increasing, also in the paediatric population[2].

To date, there is no strong evidence for the safety of administration of subsequent COVID-19 vaccine doses after C-VAM. Therefore, the CDC working group continues to recommend avoidance of the sequential COVID-19 vaccine doses (mRNA and other vaccine types) after the development of C-VAM.

CONCLUSIONS

COVID-19 vaccination-associated myocarditis in the paediatric population is currently a rare disorder, but its prevalence may increase in the future. It is advisable to consider this diagnosis in patients presenting with chest pain after vaccination, even if there were no side effects after the administration of the first and second COVID-19 vaccine doses. Despite the mild clinical course of the disease, further follow-up is recommended because cardiac MRI abnormalities may persist.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contributions

Original concept of study: MP, BW. Collection, recording and/or compilation of data: MP, MBF. Analysis and interpretation of data: MP, MBF, BW. Writing of manuscript: MP. Critical review of manuscript: BW. Final approval of manuscript: BW.

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