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ORIGINAL ARTICLE

Short-term outcome of late gadolinium changes detected on cardiovascular magnetic resonance imaging following coronavirus disease 2019 Pfizer/BioNTech vaccine-related myocarditis in adolescents

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Abstract

Background Rare cases of cardiac inflammation following vaccination for severe acute respiratory coronavirus 2 (SARS-CoV-2) have been reported.

Objective To study paediatric patients with clinical findings of acute inflammation post coronavirus disease 2019 (COVID-19) Pfizer/BioNTech vaccination using cardiovascular magnetic resonance imaging (MRI) in acute and subacute phases.

Materials and methods We enrolled adolescents younger than 18 years who presented at one of two institutions between July 2021 and August 2022 with clinical and laboratory findings of acute myocarditis shortly following COVID-19 Pfizer/BioNTech vaccination. They all underwent cardiovascular MRI using the institutional myocarditis protocol.

Results Five adolescents (four boys) underwent eight scans between 3 days and 109 days (mean 49 days) after the onset of symptoms following COVID-19 vaccination. Myocardial oedema appeared on short tau inversion recovery (STIR) T2-weighted images in three adolescents at presentation (3–12 days after symptom onset). In these children, the myocardial oedema/acute inflammation had resolved at follow-up cardiovascular MRI (53–68 days after first MRI). However, in all three adolescents, a persistent area of late gadolinium enhancement was evident at follow-up, suggesting post-myocarditic fibrosis. One adolescent scanned only once, 66 days after being symptomatic, had no acute inflammation but persistent fibrotic changes. This last adolescent, who underwent the first scan 109 days after symptom onset, had findings compatible with an episode of previous myocarditis, with mild ongoing regional myocardial oedema/inflammation.

Conclusion This study on post-vaccine myocarditis demonstrates residual lesions with persistent areas of late gadolinium enhancement/myocardial fibrosis with ongoing myocardial oedema after resolution of the initial myocardial oedema a few weeks after Pfizer/BioNTech vaccination. There is an urgent need to recognise and fully investigate the outcome of post-vaccination myocarditis.

Keywords Adolescents · Cardiovascular · Children · Coronavirus disease 2019 · Magnetic resonance imaging · Messenger ribonucleic acid · Myocarditis · Vaccination

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Introduction

Myocardial inflammation and fibrosis have been well-documented after coronavirus disease 2019 (COVID-19) infection in cardiovascular magnetic resonance imaging (MRI) studies [1]. Rare cases of cardiac inflammation following severe acute respiratory coronavirus 2 (SARS-CoV-2) vaccination have also been reported, mostly 2–5 days after the second vaccination [2–5]. The most affected population seems to be healthy male adolescents [2, 6]. The estimated rate varies widely, with the highest reported between 94 per million in 16–17-year-olds to 162.2 per million in 12–15-year-olds [5]. However, a generally accepted and more realistic estimated rate appears to be about 15 per million [7, 8]. The aim of this study was to explore the role of cardiovascular MRI in diagnosis and short-term follow-up in paediatric patients after COVID-19 Pfizer/BioNTech vaccination to understand better the extent and type of myocardial involvement.

Materials and methods

We enrolled adolescents younger than 18 years who presented at one of two institutions between July 2021 and August 2022 with clinical and laboratory findings of acute myocarditis shortly following COVID-19 Pfizer/BioNTech vaccination. All underwent cardiovascular MRI confirming the myocarditis process.

The study conforms to the ethical guidelines of the 1975 Declaration of Helsinki and the study protocol was approved by the local research ethics committees. The adolescents were scanned at 1.5-tesla (T) on an Aera/AvantoFif scanner (Siemens, Erlangen, Germany).

Cardiovascular MRI using our institutional myocarditis protocol was performed. The cardiovascular MRI protocol included left and right ventricular long-axis and outflow tract cines; 4-chamber view cine and short-axis cine stack. A short tau inversion recovery (STIR) sequence was obtained in the same views to explore myocardial oedema/inflammation. Native T1 mapping was performed using 3(3)5 modified Look-Locker imaging (MOLLI) single-shot balanced steady-state free precession (bSSFP) sequence; T2 mapping was also based on a single-shot sequence (1.5-T bSSFP, 3-T spoiled gradient echo [GRE]). We used institutional values from healthy individuals as a reference: native T1 normal range was 975–1,065 ms. T2 values were considered abnormal if they were > 60 ms at 1.5 T. Late gadolinium enhancement images were acquired after administration of intravenous gadopentetate dimeglumine (Schering, Berlin, Germany) at a dose of 0.1 mmol/kg in identical short-axis planes to cine images with a breath-hold inversion-recovery gradient echo sequence. We used Circle Cardiovascular Imaging CVI[42] software version 5.12 (Calgary, Canada) for analysis.

Results

Five adolescents (ages 13–16 years, 4 boys) fulfilled the criteria and were included in the study. All adolescents presented with chest pain 2–5 days after vaccination with Pfizer/BioNTech vaccine (two after second dose, three after first dose). Three adolescents were previously healthy. One had COVID-19 infection 2 months and 4 months prior to vaccination, and another had a history of sarcoidosis (treated with methotrexate) and congenital hearing loss.

Altogether, eight cardiovascular MRI scans (three adolescents had two scans and two had one scan each) were performed between 3 days and 109 days (mean 49 days) after the onset of symptoms following COVID-19 vaccination.

Demographic and clinical data are shown in Table 1; electrocardiographic (ECG) and echocardiographic data are in Table 2. Cardiovascular MRI findings are displayed in Table 3 (Figs. 1, 2, 3, 4 and 5). Native T1 and T2 imaging was available in four of the five adolescents.

All adolescents were treated as outpatients; none required hospital admission. They were treated with non-steroidal anti-inflammatory medication and rest; one was also prescribed betablockers. Patient 1 was a race car driver. He was extensively examined and underwent a stress echocardiogram because he was very keen to restart racing as soon as possible. At 4 weeks, stress echocardiography revealed normal left ventricular function with no regional motion abnormalities and appropriate augmentation of the left ventricular ejection fraction during exercise from 56% to 77%. The boy remained asymptomatic during the test. ECG showed T wave inversion in the infero-anterior leads on standing and during exercise without ST depression. Another 24-h Holter ECG was completely normal. The boy was allowed to resume exercise and restart car racing 6 weeks after his initial episode and remained asymptomatic.

Interestingly, patient 2, who had significant persistent late gadolinium enhancement areas (the most prominent among the five patients) 3 months after the first cardiovascular MRI, presented with similar symptoms as the

Table 1 Demographic, clinical and laboratory data

Patient number	Age, years	Sex	Ethnicity	Troponin, ng/L (normal value < 19.8 ng/L)	Clinical presentation	Development of symptoms following vaccine	History
1	16	Male	White	1,065	Fatigue and 3 days of intermittent chest pain	5 days after 2nd dose	Highly competitive automobile racer, no previous relevant medical history
2	16	Male	White	3,301	Chest pain, fever and shivering	2 days after 2nd dose	Previously healthy
3	13	Male	White	6,928	Severe chest pain	3 days after 1st dose	Previously healthy
4	15	Male	White	2,300	Fever, myalgia and chest pain	3 days after 1st dose	Congenital hearing loss, history of sarcoidosis treated with methotrexate
5	14	Female	White	360	Nausea and central chest pain	3 days after 1st dose	History of COVID-19 infection 2 months and 4 months prior to vaccination

COVID-19 coronavirus disease 2019

other adolescents but had elevated ST segments in inferolateral leads and impaired left ventricular function. This contrasted with the others, whose ECG and echocardiographic findings were either normal or showed only minor abnormalities.

The symptoms of patient 5 gradually improved, although 2 weeks after the onset of symptoms she still intermittently experienced central "achy" chest pain, 4/10 in severity, which was associated with deep breathing and sometimes eating. She could walk up three flights of stairs before experiencing symptoms. She was the only patient who had mild ongoing inflammation even 3.5 months after vaccination.

Discussion

We report five cases of Pfizer/BioNTech vaccine myocarditis in adolescents diagnosed and followed up by cardiovascular MRI. Two other reports on cardiovascular MRI findings have been published to date [9, 10]. One reported cardiovascular MRI findings in 15 adults at 3–130 days (median 65 days) following diagnosis [9]. None of these adults had acute inflammatory changes and all had only mild findings; these included normal or mildly impaired ejection fraction of the left ventricle, normal or mildly increased T1 relaxation time and a small amount of late

Table 2 Electrocardiography (ECG) and echocardiographic data in the study cohort

Patient number	Initial ECG/24-h Holter ECG	Baseline echocardiogram
1	Sinus rhythm, HR 54 bpm, normal intervals, no ST segment changes No arrhythmia on 24-h ECG, variable ST/T changes	Low normal left ventricular systolic function with an ejection fraction at 55%
2	ST-segment elevation in leads II, III, aVF and V2-V6	Mildly reduced left ventricular function with a biplane ejection fraction of 47%. The inferolateral and lateral left ventricular walls appeared mildly hypokinetic
3	Normal	Normal
4	ST elevation in inferolateral leads, 24-h ECG normal	Normal
5	Sinus rhythm with low voltage in the limb leads, especially inferiorly without clear ST segment changes	Normal

bpm beats per minute, *HR* heart rate

Table 3 Cardiovascular MRI data of the study cohort at presentation and follow-up

Patient	Cardiovascular MRI findings at presentation					Cardiovascular MRI findings at follow-up					
	Volumes, function	STIR images	LGE	Native T1 mapping	Native T2 mapping	Time since symptoms	Volumes, function	STIR images	LGE	Native T1 mapping	Native T2 mapping
1 (Fig. 1)	Normal biventricular volumes and ejection fraction	Focal subepicardial/mid-wall myocardial oedema in basal inferolateral wall	Myocardial enhancement in same area	Normal mean values at basal (939 ms) and mid-ventricular level (944 ms) (T1 mapping not acquired through pathological area)	Normal mean values at basal (44 ms), midventricular (44 ms) and apical (47 ms) levels (T2 mapping not acquired through pathological area)	10 weeks	Normal biventricular volumes and ejection fraction	Negative	Small persistent area of subepicardial/mid-wall enhancement in the basal inferolateral wall	Normal mean values at basal (972 ms) and mid-ventricular (947 ms) levels	Normal mean values at basal (45 ms), midventricular (44 ms) and apical (43 ms) levels
2 (Fig. 2)	Normal biventricular volumes and ejection fraction	Extensive subepicardial/mid-wall myocardial oedema of the lateral wall from basal level to the apex	Myocardial enhancement in the same area	NA	NA	3 months	Normal biventricular volumes and ejection fraction	Negative	Extensive persistent area of subepicardial/mid-wall enhancement in the inferolateral wall from base to apex	NA	NA
3 (Fig. 3)	Normal biventricular volumes and ejection fraction	Myocardial oedema/inflammation in the basal inferior wall	Myocardial enhancement in the same area	Normal mean values at basal (939 ms) and mid-ventricular (944 ms) levels	Mildly increased T2 values at basal inferior wall (66 ms), mean value over the whole SAX 47 ms	2 months	Normal biventricular volumes and ejection fraction	Negative	Small region of residual subepicardial fibrosis limited to the basal inferior wall	Normal mean T1 values over the whole SAX (1,044 ms)	Normal mean T2 values (48 ms over the whole SAX)
4 (Fig. 4)	NA	NA	NA	NA	NA	66 days	Normal biventricular volumes and ejection fraction	Negative	Patchy subepicardial/mid-wall fibrosis in the basal-to-apical lateral wall and subtle mid-wall fibrosis in the apical septum	Normal mean values at basal (984 ms) and mid-ventricular (969 ms) levels (not acquired through LGE area)	Normal mean values 44–46 ms throughout the SAX
5 (Fig. 5)	NA	NA	NA	NA	NA	109 days	Normal biventricular volumes with normal ejection fraction	Myocardial oedema/inflammation limited to the basal inferoseptum and probably in the basal inferolateral wall	Subepicardial fibrosis in the LV basal lateral wall a subtle mid-wall fibrosis in the mid septum	Normal basal segment mean value 1,000 ms, midventricular segments mean value 1,008 ms	Normal mean T2 values (46–50 ms over the whole SAX)

LGE late gadolinium enhancement, *LV* left ventricular, *NA* not available, *SAX* short-axis stack, *STIR* short tau inversion recovery

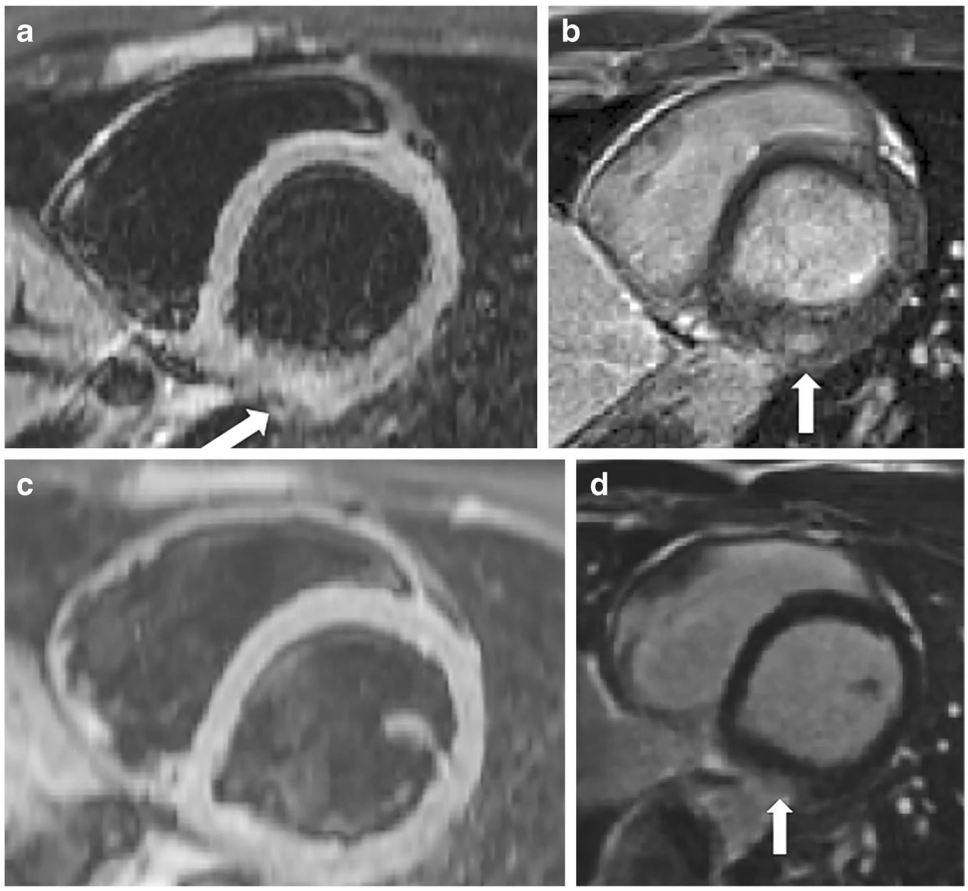

Fig. 1 Cardiovascular MRI in a 16-year-old boy, patient 1. **a, b** Presentation. Short-axis images show focal subepicardial/mid-wall myocardial oedema in the basal inferolateral wall on short tau inversion recovery (STIR) image (**a**, *arrow*) and enhancement in the same area on late gadolinium enhancement image (**b**, *arrow*). **c, d** Follow-up at 10 weeks. Short-axis images show no oedema/acute inflammation on STIR image (**c**), but there are persistent late gadolinium enhancement areas (**d**, *arrow*)

gadolinium enhancement (median 2%, range 0–15%) in 13/15 [9]. Most of the adults, as in our cohort, were males and the most frequent symptom was chest pain, mainly after the second dose of vaccine [9].

The other study documented cardiovascular MRI findings in 15 children (median age 15 years) hospitalised with myocarditis after receiving the BNT162b2 (Pfizer) vaccine [10]. Cardiovascular MRI findings were described as consistent with myocarditis in 13 children: late gadolinium enhancement in 12, regional hyperintensity on T2-weighted imaging in 2, elevated extracellular volume fraction in 3 and increased global native T1 in 2 [10]. Ten of these children underwent follow-up cardiovascular MRI at a median 92 days (range 76–119 days) after hospital discharge. Late gadolinium enhancement was persistent in 80% of the children but improved in all of them. Abnormal left ventricular global T1, which was present in two children at presentation, normalised in both on follow-up [11]. The drawback of both studies is that acute inflammation and myocardial oedema were not established in the acute phase. Given that the follow-up cardiovascular MRI in the second study documented improvement of late gadolinium enhancement findings, it is suggested that there was acute inflammation at presentation, although diagnosed only in two children [10].

In the present study, we showed that all the adolescents had acute inflammation/oedema at presentation, which healed within a few weeks. Consistent with the other studies, late gadolinium enhancement changes were still present a few weeks after vaccination, which in the setting of absence of acute inflammation is highly suggestive of fibrotic change. Surprisingly, the last patient, who had her first cardiovascular MRI 109 days after the onset of symptoms following vaccination, still had a small area of ongoing inflammation. It is therefore important to carefully investigate symptomatic children following vaccination, and long-term follow-up of the late gadolinium enhancement changes is recommended.

Although prognostic significance of non-ischaemic myocardial fibrosis in children with normal left ventricular volumes and ejection fraction showed low risk for sudden cardiac death, the presence of late gadolinium enhancement was associated with hospitalisation for suspected myocarditis and symptomatic ventricular tachycardia [12]. Similar long-term follow-up studies are warranted for these children following COVID-19 vaccination.

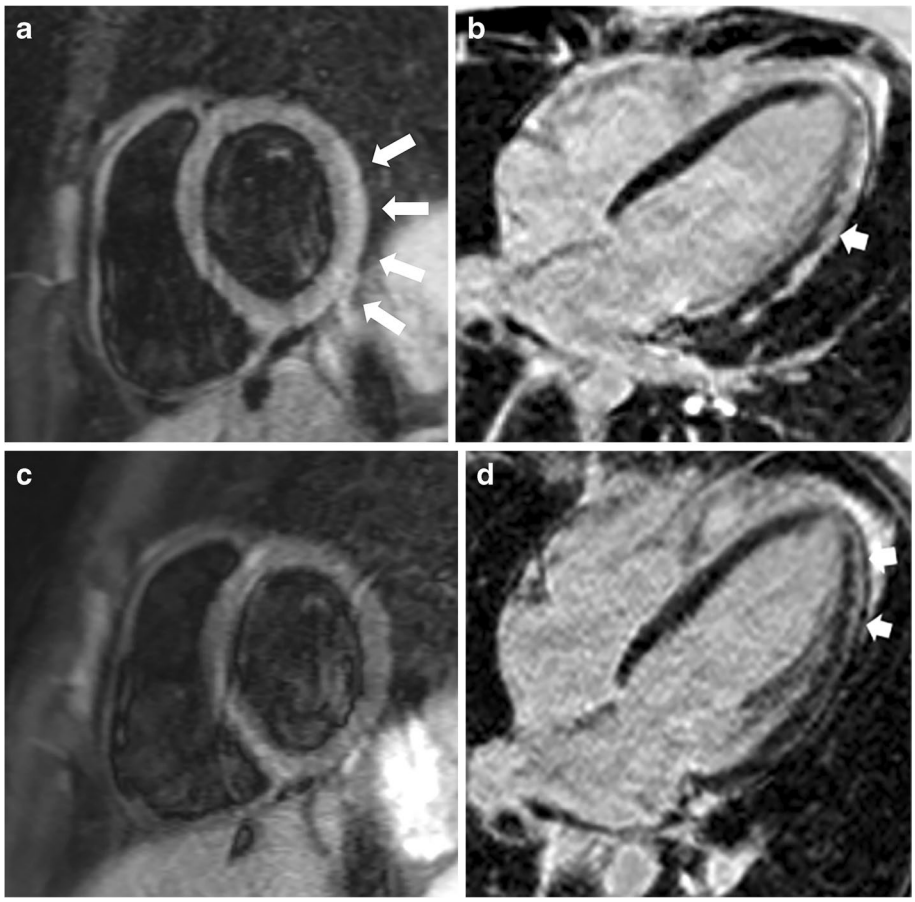

Fig. 2 Extensive subepicardial/mid-wall myocardial oedema of the lateral wall from base to apex in a 16-year-old boy, patient 2. **a, b** Presentation. Short tau inversion recovery (STIR) T2-weighted images show myocardial oedema/acute inflammation (**a**, short-axis view, *arrows*) and myocardial enhancement on late gadolinium enhancement image in the same area (**b**, 4-chamber view, *arrow*). **c, d** Follow-up at 3 months. Short-axis STIR image shows complete resolution of myocardial oedema/acute inflammation (**c**) but 4-chamber late gadolinium enhancement image shows an extensive persistent area of subepicardial/mid-wall enhancement in the inferolateral wall from base to apex (**d**, *arrows*)

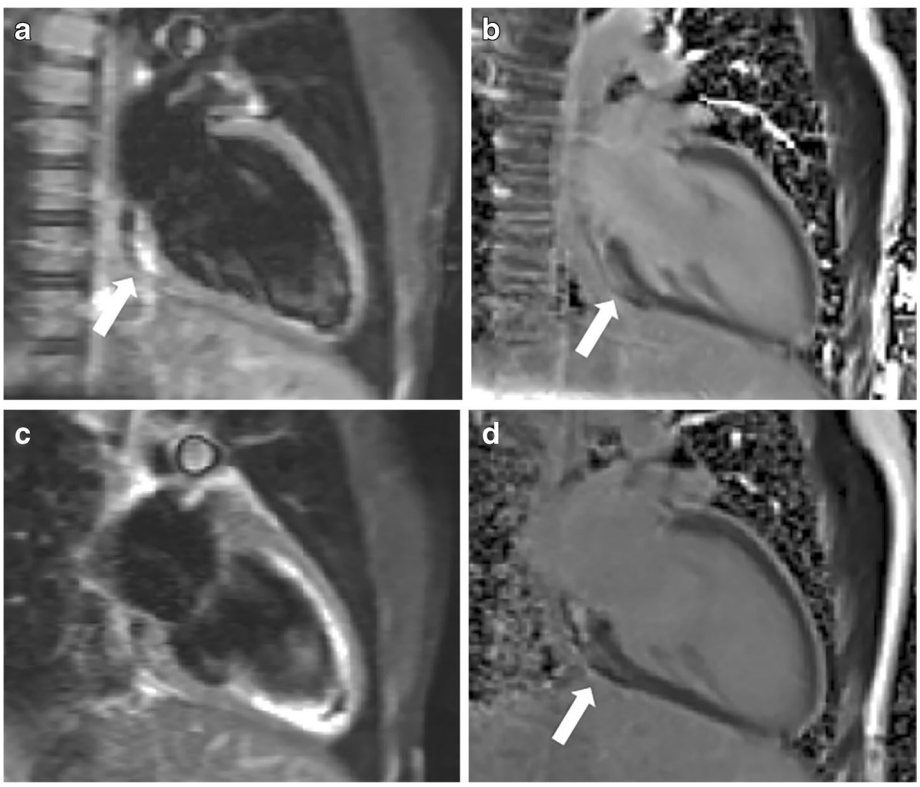

Fig. 3 Cardiovascular MRI in a 13-year-old boy, patient 3. **a, b** Presentation. Vertical long-axis short tau inversion recovery (STIR) image (**a**) shows myocardial oedema/inflammation (*arrow*) and subepicardial enhancement. Late gadolinium enhancement vertical long-axis image (**b**) shows the basal inferior wall at the time of presentation (*arrow*). **c, d** Follow-up at 2 months. Repeat cardiovascular MRI (*black circle* outlines the left pulmonary artery) shows no myocardial oedema/acute inflammation (**c**, vertical long-axis view, STIR image). A small region of residual subepicardial fibrosis is limited to the basal inferior wall (**d**, vertical long-axis view, late gadolinium enhancement image, *arrow*)

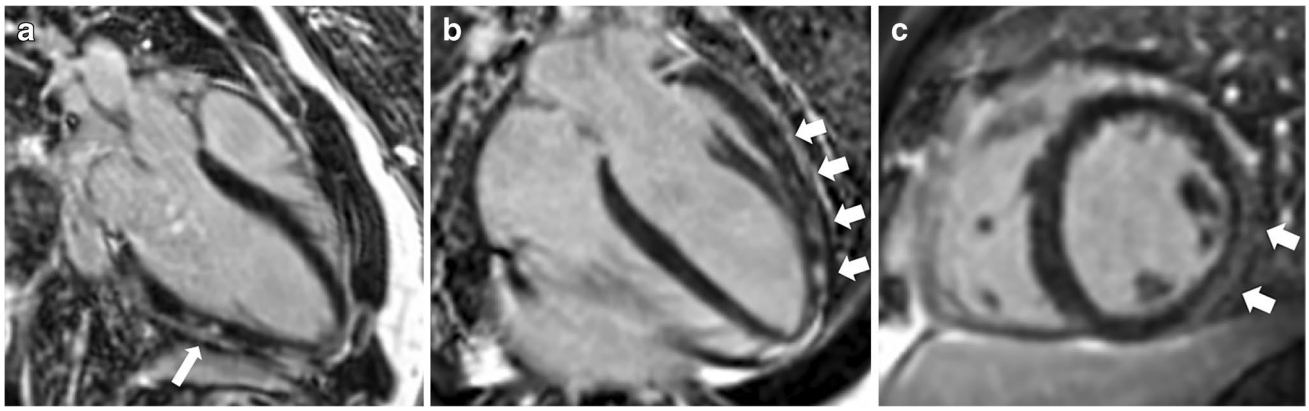

Fig. 4 Cardiovascular MRI in a 15-year-old boy, patient 4. **a–c** Late gadolinium enhancement images show patchy subepicardial/mid-wall fibrosis in the basal-to-apical lateral wall in keeping with a previous episode of myocarditis (**a**, left-ventricular outflow tract; **b**, 4-chamber view; **c**, short-axis view) (*arrows*)

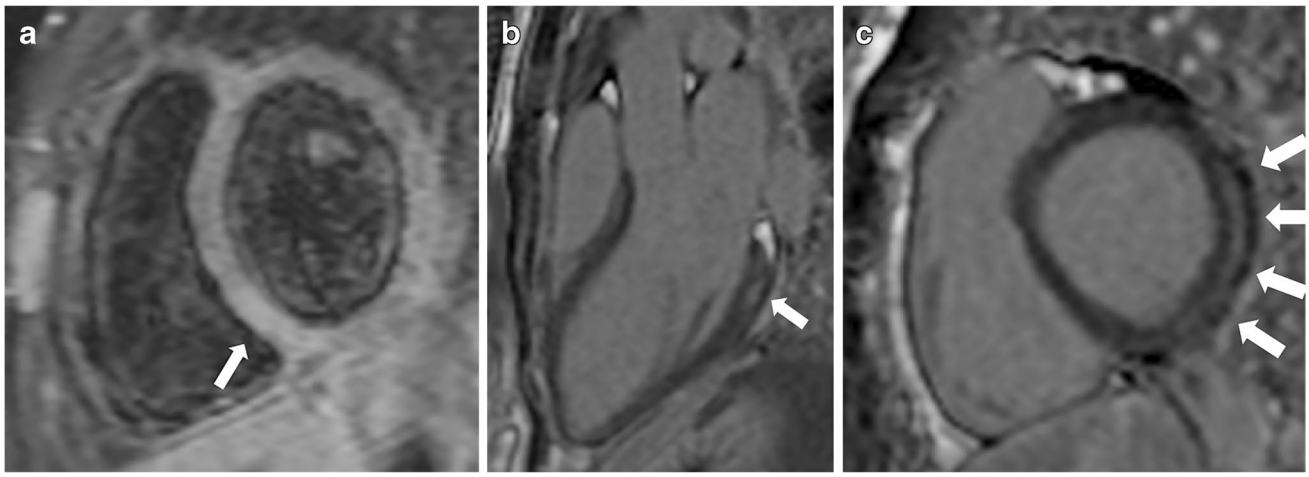

Fig. 5 Evidence of myocardial oedema/inflammation in a 14-year-old girl, patient 5 at 109 days follow-up. **a** Short-axis short tau inversion recovery (STIR) image shows oedema/inflammation limited to the basal inferoseptum and probably in the basal inferolateral wall (*arrow*). **b, c** Late gadolinium enhancement images show subepicardial fibrosis in the left ventricular basal lateral wall on left ventricular outflow tract (**b**) and short-axis (**c**) views (*arrows*)

Conclusion

This study shows short-term outcomes of post-COVID-19 Pfizer/BioNTech vaccine myocarditis, demonstrating residual lesions with persistent areas of late gadolinium enhancement after resolution of the initial myocardial oedema on T2-W STIR images, which strongly suggests myocardial fibrosis. There is now an urgent need to recognise and fully investigate the long-term outcome of post-vaccination myocarditis to improve our understanding of pathogenesis, guide treatment decisions and prevent negative sequelae in these children.

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Declarations

Conflict of interest None

References

1. Puntmann VO, Carerj L, Wieter I et al (2020) Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol 5:1265–1273
2. Kim HW, Jenista ER, Wendell DC et al (2021) Patients with acute myocarditis following mRNA COVID-19 vaccination. JAMA Cardiol 6:1196–1201
3. Barda N, Dagan N, Ben-Shlomo Y et al (2021) Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. N Engl J Med 85:1078–1090

4. Diaz GA, Parsons TG, Gering SK et al (2021) Myocarditis and pericarditis after vaccination for COVID-19. JAMA 326:1210–1212
5. Høeg TB, Krug A, Stevenson J, Mandrola J (2021) SARS-CoV-2 mRNA vaccination-associated myocarditis in children ages 12–17: a stratified national database analysis. MedRxiv. https://doi.org/10.1101/2021.08.30.21262866
6. Wise J (2021) Covid-19: should we be worried about reports of myocarditis and pericarditis after mRNA vaccines? BMJ 373:n1635
7. Medicines and Healthcare Products Regulatory Agency (2021) Coronavirus (COVID-19) vaccines adverse reactions. GOV.UK. https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting. Accessed 02 Dec 2022
8. UK Health Security Agency (2022) Myocarditis and pericarditis after COVID-19 vaccination: clinical management guidance for healthcare professionals. GOV.UK. https://www.gov.uk/government/publications/myocarditis-and-pericarditis-after-covid-19-vaccination/myocarditis-and-pericarditis-after-covid-19-vaccination-guidance-for-healthcare-professionals. Accessed 02 Dec 2022
9. Shiyovich A, Witberg G, Aviv Y et al (2022) A case series of myocarditis following third (booster) dose of COVID-19 vaccination: magnetic resonance imaging study. Front Cardiovasc Med 9:839090
10. Dionne A, Sperotto F, Chamberlain S et al (2021) Association of myocarditis with BNT162b2 messenger RNA COVID-19 vaccine in a case series of children. JAMA Cardiol 6:1446–1450
11. Hadley SM, Prakash A, Baker AL et al (2022) Follow-up cardiac magnetic resonance in children with vaccine-associated myocarditis. Eur J Pediatr 181:2879–2883
12. Lota A, Tsao A, Owen R et al (2021) Prognostic significance of nonischemic myocardial fibrosis in patients with normal LV volumes and ejection-fraction. JACC Cardiovasc Imaging 14:2353–2365