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Recurrent HHV-7 myocarditis in a 16-year-old boy

Nawrotowe zapalenie mięśnia sercowego o etiologii HHV7 u 16-letniego chłopca

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Abstract

Recurrent myocarditis is very rare, with most cases reported in adults. We present a case of a 16-year-old boy with 2 episodes of myocarditis 4 months apart. The aetiological factor of the first episode was not detected, whereas the second episode was caused by HHV-7 infection, which, according to literature reports, is an extremely rare cause of myocarditis. We described the evolution of changes in electrocardiography, changes in echocardiography and magnetic resonance as well as laboratory abnormalities, with particular focus on the differences between the first and the second episode. The patient was treated with bed rest and enalapril. Metoprolol was included during the second episode. The left ventricular function returned to normal after both episodes. This rare course of disease indicates the need for further clinical follow-up and periodic cardiac check-up in children considered to be cured.

Keywords: myocarditis, recurrent nature, children

Streszczenie

Nawrotowe zapalenie mięśnia sercowego występuje bardzo rzadko, a większość opisanych przypadków dotyczyła osób dorosłych. W niniejszej pracy przedstawiono przypadek 16-letniego chłopca, u którego wystąpiły 2 epizody zapalenia mięśnia sercowego w odstępie 4 miesięcy. Przy pierwszym epizodzie nie wykryto czynnika etiologicznego, natomiast drugi epizod był wywołany przez infekcję wirusem HHV7 – według dostępnego piśmiennictwa uważanym za niezwykle rzadki czynnik etiologiczny zapalenia mięśnia sercowego. Opisano ewolucję zmian w elektrokardiografii, zmiany w badaniu echokardiograficznym i rezonansie magnetycznym oraz odchylenia w badaniach laboratoryjnych, zwracając szczególną uwagę na różnice pomiędzy pierwszym a drugim epizodem. U opisywanego pacjenta w leczeniu zastosowano reżim łóżkowy oraz enalapril, a przy drugim epizodzie także metoprolol. Po obydwu epizodach zaobserwowano powrót funkcji lewej komory do normy. Ten rzadki przebieg choroby wskazuje na konieczność dalszej obserwacji klinicznej i okresowej kontroli kardiologicznej dzieci uznawanych za wyleczone.

Słowa kluczowe: zapalenie mięśnia sercowego, charakter nawrotowy, dzieci

INTRODUCTION

Myocarditis is an inflammatory disease of varied aetiology, mainly caused by infections and much less often by autoimmune processes or toxic agents. The inflammatory process mainly involves cardiomyocytes, but also the interstitial tissue and vessels. The course of the disease can be either fulminant or oligo- to asymptomatic; it may mimic other cardiological diseases, e.g. acute coronary syndrome, in older children. In addition to physical examination and medical history, electrocardiography (ECG) (sometimes with ST-segment changes suggesting acute coronary syndrome), echocardiography (ECHO), laboratory work-up (mainly troponins as markers of myocardial damage) as well as cardiovascular magnetic resonance (CMR), which is increasingly used to confirm myocarditis, are also of diagnostic importance. The course of the disease is usually mild in this age group. Patients are recommended bed rest with continuous monitoring of ECG and cardiovascular efficiency parameters. The treatment is mainly intended to prevent further cardiomyocyte damage, with common use of angiotensin-converting-enzyme inhibitors (ACEi) and beta-blockers (in some patients with tachycardia or arrhythmia)[1]. Also, intravenous immunoglobulins were shown to be beneficial in fulminant myocarditis[2,3]. Patients are usually discharged home after a few to several days with recommendations to report for periodic cardiac check-up and to limit physical exercise. Complete myocardial regeneration, which is indicated by follow-up imaging performed after a few months, is observed in most patients. The patients may then resume their previous lifestyles. According to literature, recurrent myocarditis, which occurred in our patient, is very rare in the paediatric population.

CASE REPORT

A 16-year-old boy with no previous chronic diseases reported to primary health care clinic with a several-day history of burning chest pain, preceded by symptoms of acute gastroenteritis. Additionally, he noticed a decrease in exercise tolerance during his last sports training. On admission, the boy was in good overall condition, with no symptoms. Physical examination showed no significant abnormalities. ECG was normal. Laboratory tests showed positive markers of myocardial damage: troponin I was 423 ng/L (reference up to 19 ng/L), while the other findings, including inflammatory parameters and the N-terminal pro-brain natriuretic peptide (NT-proBNP), were normal. ECHO detected physiological amounts of fluid in the pericardial sac, slightly reduced left ventricular contractility (ejection fraction, EF = 53%); the size of the heart chambers, left ventricular wall thickness and mass were normal (left ventricular internal diastolic diameter, LVIDd: 53 mm – Z-score 0.4; interventricular septum in diastole, IVSd: 0.75 cm – Z-score –0.47; left ventricular posterior wall in diastole, LVPWd: 0.75 cm – Z-score –0.15; left ventricular mass, LVM: 145 g – Z-score –0.41). A suspicion of myocarditis was raised and CMR was performed, which showed signs of myocardial oedema in T2-weighted images in the basal inferior and basal inferolateral segments as well as the medial inferolateral and apical inferior and lateral segments. This image met the magnetic resonance imaging criteria for active myocarditis. The treatment was based on bed rest and enalapril. The patient was hospitalised in the Department for 15 days. During hospitalisation, evolution of the ECG was observed: ST-segment elevation of up to 3 mm in leads V2–V5, 1 mm in leads II, III, aVF as well as positive-negative T waves in leads V5–V6 on day 2 after admission. Also, inversion of T waves in leads II, III and aVF was observed in the days that followed. ECG on discharge showed a return of the ST segment in precordial leads to the isoelectric line, inverted T-waves in the limb leads and negative T-waves in leads V5 and V6. Point-of-care monitoring and Holter ECG showed no arrhythmia. After 10 days of hospitalisation, troponin levels normalised, and the pre-discharge ECHO showed normal left ventricular contractility and left ventricular size (EF = 67%, LVIDd 51 mm – Z-score +0.58). A follow-up (including CMR) in the Department was planned after 6 months, continuation of enalapril and well-balanced lifestyle were recommended until next follow-up.

After 4 months, the boy was readmitted to the Department in the emergency mode. He developed febrile upper respiratory tract infection several days before admission. Severe stabbing and burning retrosternal pain and numbness in the left hand occurred during the night on the day of admission. On admission, the boy was in fairly good overall condition, but he reported chest pain. Physical examination showed symptoms of upper respiratory infection and quiet heart sounds, without signs of heart failure. Laboratory work-up showed higher (compared to the first episode) myocardial damage markers (troponin I 3,891.9 ng/L) as well as increased inflammatory markers: leukocytosis 12.88 × 10^3/μL with neutrophil differential count, C-reactive protein (CRP) 7.7 mg/dL (reference up to 1 mg/dL), and high levels of NT-proBNP (3,542 pg/mL). ECG showed non-specific disturbances of intraventricular conduction in leads V1–V2 and ST elevation up to 3 mm in leads II, III, V2–V5. ECHO showed a spherical left ventricle with more severely impaired contractility compared to the first episode (EF = 48%); the size of heart chambers, wall thickness and left ventricular mass were within the limits of normal (LVIDd 56.2 mm – Z-score +0.93; IVSd 0.83 cm – Z-score 0; LVM 170 g – Z-score +0.34), physiological amounts of fluid in the pericardial

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sac were detected. Point-of-care monitoring and Holter ECG showed arrhythmia – single premature ventricular beats and several pairs. Metoprolol was included. CMR showed signs of myocardial oedema in the basal inferoseptal, inferior and inferolateral, medial inferolateral and inferior and lateral apical segments – the extent of myocardial involvement by the inflammatory process was therefore slightly larger than in the previous examination during the first episode of myocarditis. Furthermore, the left ventricle was larger than in the first CMR (end-diastolic volume, EDV was 195 mL, which is 95 percentiles for age, height and body weight, compared to 180 mL during previous imaging), and the LVM was lower compared to the previous episode (130 g vs. 114 g, reference: 109–186 g).

Serum virology showed human herpesvirus 7 (HHV7) DNA. The patient required longer hospital stay during the second episode – he was discharged after 20 days. The levels of troponins and NT-proBNP returned to normal. ECHO on discharge showed 59% EF (lower compared to previous episode), the size of heart chambers and wall thickness were normal. There were no significant changes in ECG during hospital stay. ECG performed several weeks after discharge showed no abnormalities in the repolarisation period. The boy remains under cardiac supervision. He is still on enalapril and metoprolol. Currently, the patient reports no symptoms and has good tolerance of mild physical exercise. However, full physical activity will not be possible until the next follow-up CMR and exercise stress test.

DISCUSSION

Myocarditis is relatively uncommon among children (1–2/10,000 children annually). Recurrent myocarditis is even less common. We found only several papers on this disease published in PubMed in the last 10 years, with most case reports concerning adult patients. Several case reports of adult patients with initially suspected acute coronary syndrome, where it was only after obtaining normal image of coronary vessels in coronary angiography accompanied by contractility disorders (both global and segmental) that the diagnosis was extended to include CMR and correct diagnosis was made, have been published in literature[4–6]. One of these publications reported a case of a 29-year-old man with no history of other chronic conditions, who developed a total of 3 episodes of myocarditis at 3-month intervals. Differential diagnosis was difficult due to the coexistence of symptoms of myocarditis with the absence of detectable causes of the disease (despite extensive diagnosis for autoimmune and infectious diseases during each episode).

Viruses (with enteroviruses, adenoviruses and B19 parvovirus as well as herpesviruses, including HHV6, being most commonly identified) are the main causes of acute myocarditis. There are two subtypes of HHV6: HHV6A, which may cause direct cardiomyocyte damage, and HHV6B, which damages the endothelium of coronary vessels, causing their dysfunction. It is believed that most cases of HHV6 myocarditis have a severe clinical course, especially in infants, where mortality rates reach 75%. It is also more likely to lead to dilated cardiomyopathy compared to other aetiologies[7].

HHV7, which was detected in our patient, is considered a rare cause of myocarditis. The largest group of such patients was described by researchers from the Kütahya Dumlupınar University in Turkey. HHV7 DNA was detected by polymerase chain reaction (PCR) in 4 out of 8 children with myocarditis (diagnosed in children with a history of recent infection based on physical examination and medical history, elevated cardiac enzymes, abnormal ECG and ECHO). One of these patients was placed on the waiting list for a heart transplant, and another patient required a left ventricular assist device; the other patients achieved full recovery[8].

Recurrent myocarditis may be encountered in patients with streptococcal infections. Chikly et al. described a patient with 2 episodes of myocarditis, each during streptococcal pharyngitis[9].

It may be assumed, based on literature case reports of recurrent myocarditis, that each subsequent episode is associated with more severe symptoms and laboratory abnormalities, as well as longer recovery. A case report of a 2-year-old girl who developed 2 episodes of fulminant myocarditis 2 years apart may be used as an example. During her first episode, the girl required extracorporeal membrane oxygenation (ECMO) for 82 hours due to hemodynamic decompensation. CMR after 2 weeks showed normal left ventricular function and size. During the second episode, ECMO was continued for 373 hours, the girl developed symptoms of multiorgan failure, and left ventricular contractility did not normalise until after several months[10]. A 14-year-old boy, whose case was described by doctors from the Children's Hospital in Utah, also developed more severe abnormalities during his second episode of myocarditis. During his first episode, the maximum levels of troponins were 17.62 ng/mL (reference: up to 0.04 ng/mL), and the left ventricular EF was 55%, both of which normalised after several days. The patient experienced recurrence after 13 months, with maximum troponin levels of 28 ng/mL, and a drop in left ventricular EF to 42% (it quickly returned to normal, like in the previous episode)[11]. A similar observation can be made for our patient (a comparison of both episodes for the severity of abnormalities detected is shown in Tab. 1).

Myocardial dysfunction after myocarditis can persist, and sometimes even worsen with progression to dilated cardiomyopathy in about 25–30% of patients. Each subsequent episode causes damage to other areas of the heart muscle, as reported by Chikly et al. in a young woman

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Parameter	First episode	Second episode
WBC max (reference: 4.0–10.0 × 10^3/μL)	5.36 × 10^3/μL	12.88 × 10^3/μL
CRP max (reference: up to 1 mg/dL)	0.7 mg/dL	7.7 mg/dL
Troponin I max (reference: up to 19 ng/L)	423.4 ng/L	3,891.9 ng/L
Time to normalised troponin I	10 days	11 days
ECG changes on admission	Normal	Nonspecific intraventricular conduction disturbances in leads V1–V2 and ST elevation up to 3 mm in leads II, III, V2–V5
ECG changes on discharge	T-wave inversion in all limb leads, negative T-waves in leads V5–V6	ST elevation up to 3 mm in leads II, V1–V6
NT-proBNP max (reference: up to 125 pg/mL)	143 pg/mL	3,542 pg/mL
Length of stay	15 days	20 days
EF on admission	53%	48%
EF min	53%	48%
EF on discharge	67%	59%
LVIDd on admission (reference: up to 60 mm)	53 mm	56.2 mm
LVIDd max	54 mm	54.6 mm
Changes in CMR	Signs of myocardial oedema in the basal inferior and inferolateral, medial inferolateral as well as the apical inferior and lateral segments EF 54% LVM 130 g (reference: 109–186) EDV 180 mL (reference: 126–208)	Signs of myocardial oedema in the basal inferoseptal, inferior and inferolateral, medial inferolateral and apical inferior and lateral segments EF 54% LVM 114 g (reference: 109–186) EDV 195 mL (reference: 126–208) – 95 percentiles

CMR – cardiovascular magnetic resonance; **CRP** – C-reactive protein; **EF** – ejection fraction; **ECG** – electrocardiography; **LVIDd** – left ventricular internal diameter in diastole; **LVM** – left ventricular mass; **NT-proBNP** – N-terminal pro-brain natriuretic peptide; **WBC** – white blood cells.

Tab. 1. Additional tests during the first and second episode of myocarditis

who had 3 episodes of myocarditis spaced 8 years apart. After the first 2 episodes, EF returned to normal during several months of pharmacological treatment. However, during her third episode, EF dropped to about 45% and no improvement was seen despite several years of follow-up[9]. It may be assumed that relapses of myocarditis predispose to the persistent, unfavourable remodelling of the heart muscle.

CONCLUSIONS

We presented a case of a boy who developed 2 episodes of myocarditis spaced 4 months apart. Literature indicates that recurrent myocarditis is very rare in children. Both episodes were confirmed in CMR, which is currently a reference method for diagnosing myocarditis in most paediatric centres. Clinical manifestations included chest pains accompanied by the release of troponins and impaired repolarization on ECG. The DNA of HHV7, which is considered a rare cause of myocarditis, was detected during the second episode. Both episodes were mild and preceded by the symptoms of a febrile viral infection. However, left ventricular systolic dysfunction and ventricular arrhythmias were noted. In addition to limited physical activity, ACEi and beta-blockers were included in the treatment. Although left ventricular function returned to normal, the boy requires further cardiac follow-up due to the risk of progression to dilated cardiomyopathy.

Conflict of interest

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

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