

Myocarditis Associated with Coronavirus Disease 2019 (COVID-19) in a Pediatric Patient

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Abstract

Viral infection is one of the most important causes of myocarditis both in adult and pediatric age. We describe acute myocarditis due to SARS-CoV-2 infection in an otherwise healthy 12-years-old Caucasian boy. He was admitted because of a history of 2 days of fever, dry cough, diarrhea, abdominal pain and fatigue. In spite of a family history of COVID-19 patient strict contact, a first nasopharyngeal swab for SARS-CoV-2 RNA resulted negative. After 4 days, his clinical condition evolved, with the onset of interstitial pneumonia, as documented by chest tomography and tachycardia. Blood analysis showed an NTproBNP and TnT increasing, transthoracic echocardiography revealed normal left ventricle (LV) dimension, altered myocardial texture, diffuse hypokinesia and impaired left ventricular function. A nasopharyngeal swab tested positive for SARS-CoV-2 infection at day 6 after admission. Heart failure conventional treatment associated with heparin, glucocorticoids and Remdesivir were administered with progressive improvement of clinical and instrumental conditions. No residual heart damage was documented during the following 3 months cardiological outpatient follow-up. Although COVID-19 infection has a milder course of disease in children than in adults, severe forms of the disease may occur and myocarditis should be carefully considered in the pediatric age.

Keywords

Coronavirus Disease 19, Children, Myocarditis, Remdesivir

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by a novel enveloped RNA beta-coronavirus, named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-

CoV-2), which is responsible for the pandemic started on December 2019 in Wuhan (China) and rapidly spread worldwide [1] [2].

The typical initial signs of the disease are dry cough, fever, dyspnea, fatigue and an interstitial pattern with ground-glass opacities on chest computed tomography (CT) scans; less frequently the disease presentation is characterized by diarrhea and abdominal pain [3].

COVID-19 in pediatric patients seems to be less severe than in adults and the infection becomes symptomatic only in a minority of the affected children (less than 2%, as reported in literature); hospitalization due to pneumonia or other COVID-19 related complications are rare among children [4] [5]. According to the literature, cardiovascular involvement determining chest pain, impaired ventricular function, arrhythmias and heart failure has been reported in a minority of adult patients affected by SARS-CoV-2 infection [6]. Cardiac involvement in children has been described in case series in the context of multisystem inflammatory syndrome (MIS-C) in current or recent SARS-CoV-2 infection, possibly involving coronary artery [7].

Our report describes the occurrence of myocardial injury in a pediatric patient with COVID-19 diarrhea and pneumonia.

2. Case Presentation

An otherwise healthy 12-years-old Caucasian boy without a previous history of any cardiovascular or chronic disease, presented to the pediatric emergency department with fever, sporadic dry cough, diarrhea, abdominal pain and fatigue, lasting since the two previous days.

He denied dyspnea and chest pain. His cohabitant grandfather died for SARS-CoV-2 pneumonia 10 days before. His temperature was 38.5°C, blood pressure 100/70mmHg, heart rate 120 bpm, the oxygen saturation 100% without oxygen support. On chest auscultation there were diffuse wheezes. Blood tests revealed an increase in C-reactive protein levels (C-RP 10.7 mg/dL) and Procalcitonin (PCT 2.5 ng/mL) with normal blood cells count. A nasopharyngeal swab was performed with a negative result for SARS-CoV-2 on real-time reverse transcriptase-polymerase chain reaction assay. CT scan indicated initial interstitial pulmonary infection and antibiotic therapy with Ceftriaxone was started. On the 4th day of admission, his clinical condition worsened, with persistence of high grade fever, fatigue, abdominal pain and severe diarrhea. A second nasopharyngeal swab still resulted negative; on the blood tests further increase in C-RP levels (15.3 mg/dL) and PCT (6.3 ng/mL) were documented, together with the onset of lymphopenia, elevation of N-terminal pro-brain natriuretic peptide (NTproBNP) (1013 ng/l) and normal high-sensitive troponin T (TnT). A 12-lead electrocardiogram (ECG) showed a sinus tachycardia. Abdominal ultrasound showed adeno-mesenteritis, together with mild ascites. Transthoracic echocardiography revealed normal left ventricle (LV) dimension, altered myocardial texture, diffuse hypokinesis with an estimated LV ejection fraction (LVEF) of

40%. Twenty-four hours later the blood pressure decreased to 80/40mmHg, ECG showed T-wave inversion in V4 and flat T in V5-V6 and in the limb leads (**Figure 1**), TnT increased (30 ng/l), LVEF decreased until 30% and there was mild pericardial effusion (**Figure 2**). Therapy with inotropic agent (Milrinone) and diuretics (Furosemide and Spironolactone) for heart failure was started in association with steroids (Methylprednisolone 2 mg/kg × 3 days, then progressively

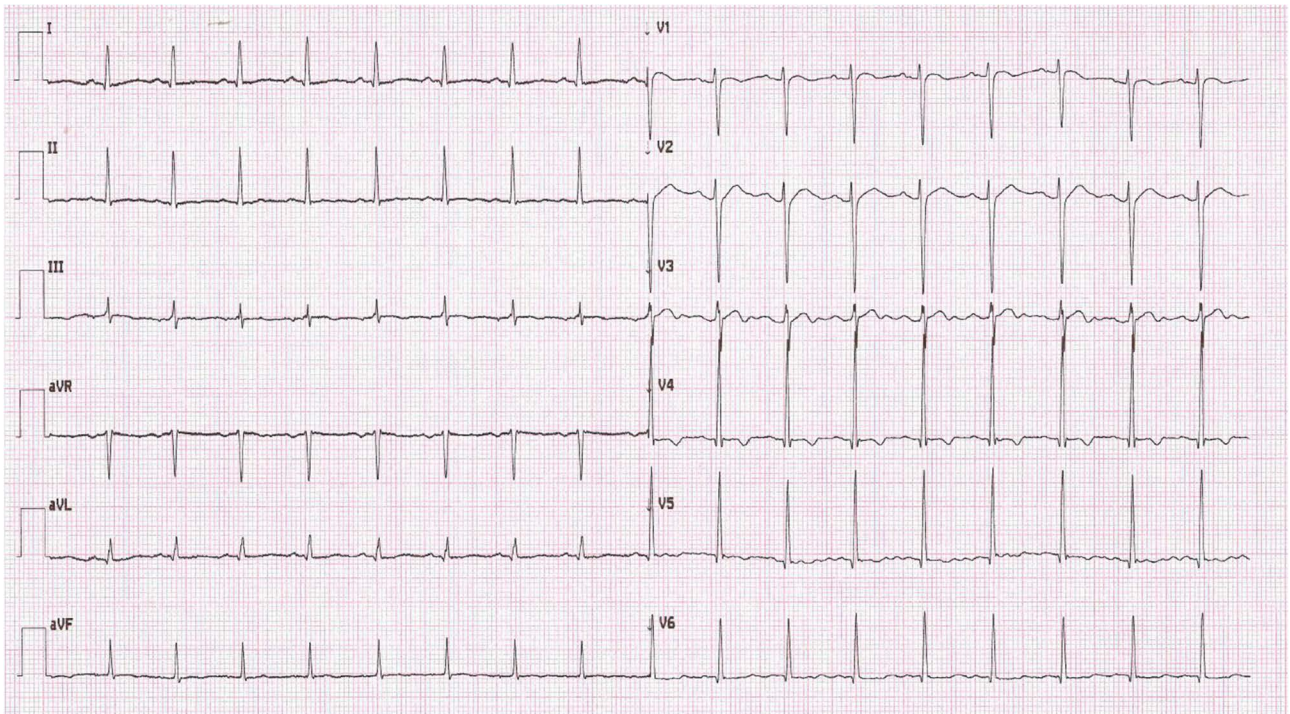


Figure 1. ECG: Electrocardiogram showing sinus tachycardia with T-wave inversion in V4 and flat T in V5 - V6 and in the limb leads.

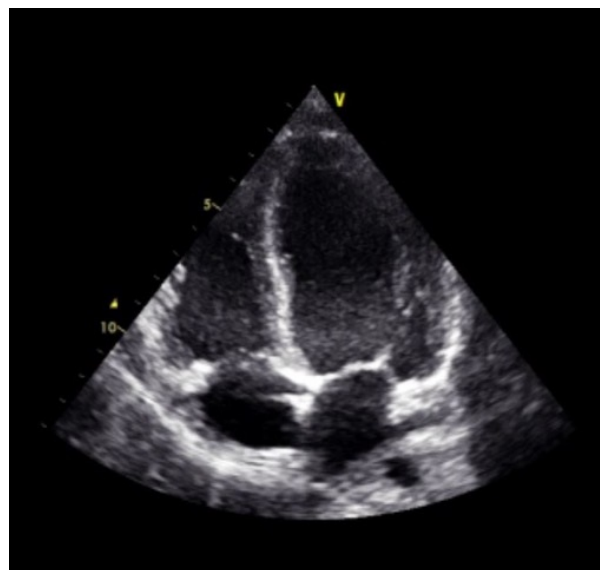


Figure 2. Echocardiography: 2D transthoracic echocardiogram (apical 4 chambers view) showing normal left ventricle dimension, altered myocardial texture and mild pericardial effusion.

tapered) and Enoxaparine (4000 U) for the evidence of altered inflammatory and coagulation markers (Ferritin 1158 ng/mL; Fibrinogen 604 mg/dL; D—dimer 3.2 mcg/mL; international normalized ratio—INR 1.24).

A nasopharyngeal swab was repeated 6 days after admission testing positive for SARS-CoV-2, while search for common cardiotropic infectious agents yielded negative results. The abdominal-chest CT scan revealed bilateral basal pulmonary ground-glass opacities (**Figure 3**), pleural effusion and ascites.

Due to the progressive worsening of the patient's clinical symptoms and the SARS-CoV-2 documented infection, antiviral therapy with intravenous Remdesivir (compassionate use) was started on the 6th day of admission for 10 consecutive days (200 mg the first day, followed by 100 mg/day). Local Ethical Committee authorization and parent consent were obtained before starting treatment.

The maximum value of TnT and of NTproBNP were 70 ng/l and 10,078 ng/L respectively (at 7th day). In the following days there was an improvement of the clinical conditions: fever and diarrhea recovered 48 hours after steroids were started. Progressive normalization of the blood tests and substantial cardiac function improvement (LVEF 55%) were also observed within the following 10 days. Inotropic agent was stopped on 8th day of admission and Enalapril was started subsequently.

He was discharged after 20 days of hospitalization in good clinical condition and hemodynamic stability, after 2 SARS-CoV-2 negative nasopharyngeal swabs were obtained. No residual heart damage was documented during the following 3 months cardiological outpatient follow-up (cardiac magnetic resonance—CMR—was also executed 1 month after discharge).

3. Discussion

Despite the relatively benign course of Covid-19 in pediatric population, since

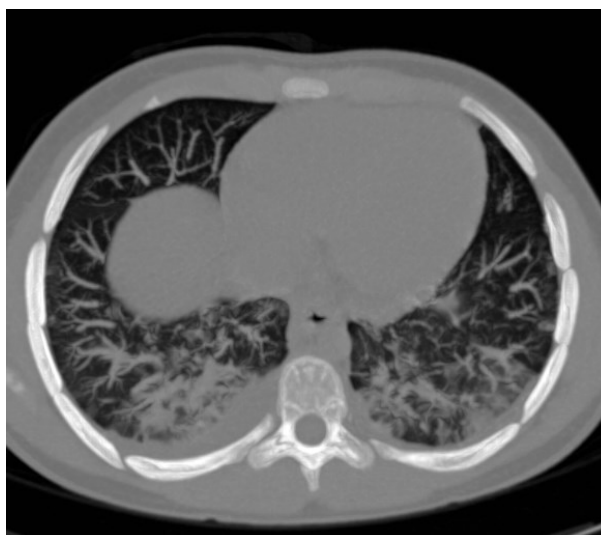


Figure 3. CT: Chest computed tomography image showing bilateral ground-glass opacities and pleural effusion.

April 2020 there have been some reports of children with MIS-C and some cardiac involvement that often resemble features of Kawasaki disease, therefore most reported cases were treated with intravenous immunoglobulin, together with steroids [8] [9]. On the other hand there are several features that distinguish MIS-C, including prominent cardiac dysfunction with elevated BNP. Our report describes SARS-CoV-2 related acute myocarditis in a pediatric patient, with no coronary damage. Pathophysiological underlying mechanism is currently uncertain.

It is known that angiotensin-converting enzyme 2 (ACE-2) is widely expressed in cardiomyocytes, cardiac fibroblasts and coronary endothelial cells and SARS-CoV-2 uses ACE-2 receptor for host cell entry. These observations might suggest that SARS-CoV-2 may directly cause myocardial injury. However, to our knowledge, there are no reports of SARS-CoV-2-RNA in the heart, to date [10].

The inflammatory activation with cytokines release syndrome, well documented in literature in COVID-19 adult patients and children, could also be considered as co-factor of heart damage [7] [8] [9] [10] [11]. The beneficial use of corticosteroids to attenuate inflammation is often used in SARS-CoV-2 critically ill adult patients [12] [13]. Such an inflammatory activation secondary to SARS-CoV-2 infection was also registered in our child. Steroid treatment indeed brought to a rapid clinical improvement in our patient, possibly confirming the key role of inflammatory cascade induced by SARS-CoV-2.

It is also known that excessive inflammation triggers platelet activation and endothelial dysfunction that may lead to thrombotic events, hence heparin was administered to our COVID-19 patient [14].

In our patient the onset symptoms were severe diarrhea and abdominal pain, which are reported in literature in 6% - 8% of pediatric cases [5]; recent published data from adult series suggest a correlation between gastrointestinal symptoms at onset of COVID-19 and severe evolution of the disease [15] as observed in our child.

As far as concern antiviral therapy, given the severity of the clinical condition, we decided to start antiviral treatment for compassionate use with Remdesivir. Up to now there are no published papers focused on antiviral therapy with Remdesivir in SARS-CoV-2 infected children. However this drug demonstrated strength in trials related to other coronavirus infections. Although SARS-CoV and SARS-CoV-2 share only 82% RNA sequence identity, their RNA-dependent RNA polymerase (RdRp) shares 96% sequence identity. Therefore, Remdesivir targeting viral RdRp proteins of SARS-CoV is likely to be effective for SARS-CoV-2 [16].

4. Conclusion

Myocardial injury due to SARS-CoV-2 infection should be considered in pediatric COVID-19 severely symptomatic patients. There are still many unanswered questions concerning the pathophysiology of MIS-C and related cardiac involvement and optimal treatment. Antiviral treatment with Remdesivir in association

with steroids could be effective in pediatric SARS-CoV-2 myocarditis.

Limitations

Despite CMR imaging represents the gold standard procedure in order to diagnose myocarditis [17], in this child it was not performed because it would have not changed the clinical management, moreover exposing healthcare staff to a further risk of infection [6]; CMR imaging was performed during outpatient follow-up for prognostic evaluation. Furthermore, endomyocardial biopsy was not performed because it is not routinely executed for myocarditis diagnosis in pediatric patients and it is usually performed in critical cases unresponsive to therapy [18].

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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