Life-threatening cardiogenic shock in a pediatric patient with SARS-CoV-2-associated myocarditis treated with remdesivir: a case description and report of similar cases from the Literature

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Case report

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Abstract

Background

Children are relatively spared from Coronavirus disease 2019 (COVID-19), but some severe cases have been reported. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children may affect the cardiovascular system. We hereby report about a case of myocarditis evolving to cardiogenic shock in a SARS-CoV-2 positive child.

Case presentation

An otherwise healthy 12-year-old patient was admitted with fever, vomiting, diarrhoea and drowsiness, without any respiratory symptoms. He was diagnosed with COVID-19 on nasopharyngeal swab. He developed hypotension and cardiogenic shock. Bedside echocardiography revealed left ventricular impairment with an ejection fraction (LVEF) below 25%. Plasmatic markers of myocardial injury were remarkably raised, as well as inflammatory biomarkers, including procalcitonin (highest recorded value: 66 ng/mL) and interleukin-6 (8209 pg/mL). The child was transferred to Intensive Care Unit and he was treated with catecholamine support, mechanical ventilation and empiric anti-infectious therapy, including broad spectrum antibiotics and the antiviral agent remdesivir. All additional microbiological investigations yielded negative results.

We observed a gradual improvement of LVEF within 5 days. A cardiac magnetic resonance confirmed the suspicion of myocarditis. After 21 days of hospitalisation, the child was discharged without *sequelae*.

Conclusions

Our hypothesis is that the child suffered from SARS-CoV-2-induced fulminant myocarditis, probably in the setting of cytokine release syndrome (CRS). The peculiarity of this SARS-CoV-2 infection is the presence of cardiac failure in a previously healthy child without a respiratory illness. The positive outcome is in line with published Literature about the overall better prognosis of COVID-19 children compared to adults. Remdesivir, an investigational antiviral therapy, may have played a role on the clinical improvement of the child.

Background

The World has recently witnessed the epidemic outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China, spreading globally and rapidly evolving into a pandemic phenomenon.

In spite of its utmost and potentially life-threatening involvement of the respiratory system, the novel coronavirus disease 2019 (COVID-19) has been recently reported as a causative factor for severe cardiac injury in adult patients.(1,2) Whether the impairment of cardiac function results from direct detrimental effect of the virus on the myocardium or should be regarded as a secondary outcome of the systemic inflammatory response elicited by COVID-19 is still debated.

Indeed, an increasing number of Authors have been highlighting the onset of severe cytokine storms in COVID-19 patients. When cytokine release syndrome (CRS) targets the cardiovascular system,(3) the clinical picture includes tachycardia, hypotension, troponin elevation, arrhythmias, QT prolongation, cardiomyopathy and acute heart failure.(3) In COVID-19 patients, all the previous clinical pictures have been described.(4) Interleukin-6 (IL-6) seems to play a pivotal role in CRS, activating complement and the coagulation pathway and inducing endothelial damage. Moreover, IL-6 has been reported to depress the myocardial function.(3,5,6) In COVID-19 patients high levels of IL-6 and C-reactive protein (CRP) appear to be negative prognostic markers.(7,8)

Most children experience no or just mild signs and symptoms of SARS-CoV-2 infection, even though severe cases, mainly occurring in patients with an underlying disease, have been described.(9–11) Pediatric COVID-19 patients may experience respiratory, gastrointestinal, neurological symptoms, but few is known about cardiovascular involvement.(9,10)

We hereby report the first pediatric case of myocarditis in a child affected by COVID-19 and presenting with cardiogenic shock.

Case Presentation

An otherwise healthy 12-year-old boy was admitted to a peripheral hospital (Lombardy – northern Italy), with complaints of fever, vomiting, diarrhoea and drowsiness for the previous three days. Though no respiratory symptoms were reported, both his parents have been presenting with cough and low-grade fever for several weeks. Patient's past medical history was unremarkable.

On admission, blood tests showed normal full blood count but raised CRP (23.4 mg/dL, reference range < 0.5) and procalcitonin (PCT – 3.3 ng/ml, reference range < 0.5). Despite negative findings at chest x-ray, based on the clinical and family history, COVID-19 was suspected and a nasopharyngeal swab was performed, showing positive result for SARS-CoV-2 infection by real-time reverse transcriptase–polymerase chain reaction (RT-PCR). Later, also nasopharyngeal swab of patient's father revealed to be positive.

Twenty-four hours later, a remarkable increase of both CRP (33.1 mg/dL) and PCT (44.22 ng/ml) prompted the collection of peripheral blood culture, the start of systemic antibiotic treatment with intravenous Ceftriaxone and patient's transferral to the Pediatric Department of our tertiary care Centre.

Upon arrival, the patient was ill-appearing, highly febrile (body temperature: 39.0°C) and tachycardic (140 beats per minute), though he presented with normal blood pressure (110/70 mmHg) and room-air pulse-oximetry (98%).

Repeated laboratory investigations showed a further worsening of inflammation markers (CRP 43.11 mg/dL, PCT 58.84 ng/mL), neutrophilia (neutrophils 12.18 x10^3/μL) and raised D-Dimer (2396 ng/mL, reference range <250), with an International Normalized Ratio (INR) of 1.4 and increased lactate (4 mmol/L). Venous gas analysis and baseline electrocardiogram provided normal results.

Given the overall worsening of both clinical and biochemical picture despite ongoing antibiotic treatment, Ceftriaxone was empirically switched to a combination of intravenous meropenem and vancomycin. In addition, antithrombotic therapy with intravenous unfractioned heparin was introduced.

In a few hours the child developed severe hypotension (blood pressure: 70/40 mmHg) and clinical signs consistent with progressive peripheral hypoperfusion, refractory to intravenous fluid resuscitation (saline solution: 20 mL/Kg in 15 minutes) and vasoactive amines infusion (norepinephrine). Urgent bedside echocardiography showed a severe decrease in ventricular systolic function, with a left ventricle ejection fraction (LVEF) of 25%, increased left ventricular dimensions with diffuse hypokinesis but retained right ventricular function. Both troponin T (TnT, 602 ng/L with reference range < 14) and N-terminal brain natriuretic peptide (NT-proBNP, 27075 pg/mL with reference range < 300) were found to be remarkably raised.

Due to a progressive deterioration of the clinical picture and the need for mechanical ventilation, invasive hemodynamic monitoring and combined norepinephrine and dobutamine infusion, the patient was transferred to our Intensive Care Unit (ICU).

As showed in figure 1, after an initial improvement, the patients experienced a steep exacerbation of both clinical and biochemical data within 48 hours. Interleukin-6 was tested at this stage and showed a peak value of 8209 pg/ml (reference range: < 7). A chest and abdomen CT scan showed radiological signs consistent with uncomplicated colitis, while pulmonary findings were unremarkable.

The patient was therefore started on antiviral treatment with remdesivir, an investigational nucleoside analogue prodrug with supposed efficacy on SARS-CoV-2, at the loading dosage of 200 mg, followed by 100 mg every 24 hours. Vancomycin was discontinued and replaced with tigecycline and clindamycin, while treatment with meropenem was continued unchanged. Support therapy including vasoactive and inotropic amines, short course hydrocortisone (due to its mineralocorticoid effect), furosemide and captopril was undertaken. With the exception of SARS-CoV-2, all the remaining microbiological investigations performed yielded negative results, including peripheral blood cultures for fungi and bacteria and serologies for cardiotropic infectious agents (echoviruses, coxsackieviruses, cytomegalovirus, adenovirus and mycoplasma) and PCR essays on blood and stool for enterovirus genus nucleic acids.

During the following days, patient's clinical condition progressively improved. Figure 1 shows how the gradual drop of inflammation and myocardial damage markers corresponded to a concomitant increase of LVEF, leading to restoration of cardiac function by the fifth day of intensive care. In two additional days' time, the patient was progressively weaned from vasoactive support and definitely extubated. The SARS-CoV-2-targeted nasopharyngeal swab and bronchoalveolar lavage performed seven days after the start of antiviral treatment showed negative results, and remdesivir was therefore discontinued.

Gadolinium-enhanced cardiac Magnetic Resonance Imaging (MRI), performed on day 13, detected an area of subepicardial delayed enhancement within the left ventricle, consistent with recent myocarditis (See figure 2 for detailed description of radiological findings).

After 21 days of hospitalization, the child was discharged with no *sequelae*.

Discussion And Conclusions

We hereby report about a 12-year-old SARS-CoV-2-positive patient who presented with biochemical and clinical signs of acute cardiac injury (raised necrosis markers, severely depressed left ventricle function) in the presence of radiological signs consistent with myocarditis and no signs of respiratory involvement.

In our opinion, several points are worthy of discussion.

Firstly, we presented a rare case of SARS-CoV-2-related cardiac involvement in childhood. Viral infections are the commonest cause of myocarditis in children(12) and myocardial involvement has already been reported in a few SARS-CoV-2-positive patients. Table 1 compares the clinical, laboratory and diagnostic features of all the cases published hereinbefore. (13–21)

Secondly, in our patient, acute onset with progressive clinical deterioration and refractory cardiogenic shock met the diagnostic criteria for fulminant myocarditis (FM).(22,23) This is not unexpected in adulthood, as 4 out of the 9 published cases involving adult patients diagnosed with myocarditis met the criteria of COVID-19-related FM (Table 1). Our case highlights that in case of rapid otherwise unexplained deterioration of clinical conditions in SARS-CoV-2-positive patients, also pediatricians should keep a high index of suspicion and deem FM as a potential diagnosis.

Other than myocarditis, myocardial infarction, disseminated intravascular coagulation (DIC)-associated damage, stress induced cardiomyopathy and CRS-associated damage have been described as possible clinical presentations of cardiac involvement in COVID-19.(4) Indeed, cardiac injury in COVID-19 probably has a multi-factorial genesis. Many Authors agree that different mechanisms may interplay leading to cardiac injury: direct viral damage on myocardial cells, overwhelming inflammation process due to cytokine storm and hypoxia due to the imbalance between increased myocardial oxygen demand and decreased pulmonary oxygen supply during acute respiratory syndrome.(1,24)

As showed in Figure 1, in our case increased TnT and NT-pro-BNP levels, as well as decreased ejection fraction at echocardiography were significantly correlated with IL-6 and CRP levels over time. Similar data have already been described in published Literature.(24) A recent meta-analysis demonstrated that elevated IL-6 values are associated with increased severity and mortality of SARS-Cov-2 disease (8) and patients treated with IL-6 inhibitors, such as Tocilizumab, have reported a clinical improvement.(25) We decided not to administer tocilizumab to our patient because clear demonstrations of the safety and clinical effectiveness of this anti IL-6 drug is currently lacking.(8,26)

As showed in table 1, both in our pediatric case and in several adult patients, cardiac failure due to myocarditis in otherwise healthy patients may occur without any associated respiratory symptoms. On the other hand, the complete lack of electrocardiographic signs found in our patients is infrequent amongst adults.

Third, there are few reports of remdesivir use in children, and none of them in patients with acute myocarditis. Remdesivir has recently been associated with some clinical benefit in adult patients with COVID-19 (27), leading the US Food and Drug Administration to issue an emergency use authorization for the treatment of COVID-19 in adults and children hospitalized with severe disease. Similarly, remdesivir has been proposed as the preferred agent in children, when antiviral treatment is regarded as potentially beneficial.(28) Nonetheless, most COVID-19 pediatric patients with either mild or severe disease described so far, recovered with supportive care only. Accordingly, ascertaining whether antiviral therapy played a central role on the clinical improvement experienced by our patient is challenging and potentially misleading.

Finally, we are aware that the present case report has some limitations. Firstly, in a highly febrile patient who presented with remarkably raised CRP and PCT, it may be argued that the cardiac impairment could be secondary to concomitant septic shock. Cardiac biopsy could have demonstrated the primary myocardial involvement, but it was contraindicated due to the procedure-related risk in a hemodynamically instable patient. However, cardiac MRI, increasingly used to diagnose myocarditis(29) on the back of the non-invasiveness of the technique, confirmed the diagnosis throughout pathognomonic findings. In addition, the lack of etiological agents other than SARS-CoV-2 identified at repeated cultures decreases the likelihood of a cryptogenic bacterial systemic infection.

Furthermore, our patient was treated with supportive therapy, empirical antibiotics and remdesivir. Assessing the relative contribution of each of these treatments and discerning between therapeutic effectiveness and natural history of the disease in an otherwise healthy child may be misleading. However, the timing of remdesivir administration suggests that it may have played a role in the positive evolution of the overall clinical picture.

In conclusion, although rare, SARS-CoV-2 infection in children may affect the cardiovascular system and result in a life-threatening disease. Pediatricians should take into account fulminant myocarditis amongst the clinical conditions elicited by COVID-19 and potentially resulting in a fatal outcome.

Abbreviations

COVID-19: Coronavirus disease 2019, CRP: C-reactive protein, CRS: cytokine release syndrome, CT: computer tomography, DIC: disseminated intravascular coagulation, FM: fulminant myocarditis, ICU: Intensive Care Unit, IL-6: Interleukin-6, INR: International Normalized Ratio, LVEF: Left ventricular ejection fraction, MRI: Magnetic Resonance Imaging, NT-pro-BNP: N-terminal brain natriuretic peptide, PCT: procalcitonin, RT-PCR: real-time reverse transcriptase–polymerase chain reaction, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, TnT: troponin T

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Written informed consent was obtained from the legal parent for publication of this case report and any accompanying images.

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

SM, LC and AC, developed the idea of the study, participated in its design and coordination and helped to draft the manuscript. SM, LC, MML and AC contributed to the acquisition and interpretation of data. MML, AC, RP, MB, GL and AB were involved in critically reviewing the manuscript. All authors read and approved the final manuscript.

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Table

EMOGRAPHIC AND CLINICAL DATA				CHEST X-RAY		CHEST CT		ECG	ECHOCARDIOGRAPHY		CARDIAC MRI		LABORATORY RESULTS				FULMINANT[a]
ge ars)	Gender	Symptoms complained	Comorbidities	Pulmonary findings	Cardiac findings	Pulmonary findings	Cardiac findings		Descriptive findings	LVEF	LV on T2 short tau inversion recovery	Gadolinium enhancement	IL-6 (pg/mL) peak	CRP (mg/dL) / PCT (ng/mL) peak	Troponin (ng/mL) at onset	Pro-BNP (pg/mL) at onset	
13	Male	Fever, vomiting, diarrhoea	No	None	None	None	None	Negative	Increased LV dimensions, diffuse LV hypokinesis	25%	Intense signal	Focal intramyocardial delayed enhancement	8209	43,11/66	0,602	27075	Yes
21	Female	Fever, cough, dyspnea, diarrhoea	No	Bilateral multifocal consolidation	Cardiac hypertrophy	Bilateral ground-glass opacification	Myocardium hypertrophy; Subendocardial perfusion defect	Multiple premature ventricular complexes	Not described	Severely impaired LFVE	Intense signal	Extensive transmural late enhancement	Not described	Not described	1.26	1929	No
53	Female	Fatigue	No	None	None	Not described	Not described	Elevated ST tract; Low voltages; T wave inversion in V1 and aVR	Diffuse dyskinesis; LV hypertrophy; Pericardial effusion	40%	Intense signal	Extensive transmural late enhancement	Not described	1.3/-	0.24	5647	Yes
53	Male	Fever, dyspnea	No	Ground-glass opacification	None	Bilateral ground-glass opacification	None	Sinus tachycardia	Diffuse dyskinesis; LV hypertrophy	32%	Not described	Not described	272	Not described	11.37	22600	Yes
59	Female	Fever, chest pain	Hypertension, degenerative cervical arthropathy, lymph-nodal tuberculosis	Vascular redistribution with no signs of primary parenchymal involvement	None	Not described	Not described	Elevated ST tract; Low voltages	*At onset*: LV hypertrophy; Pericardial effusion *Evolution*: Severe biventricular dysfunction	*AT Onset*: normal LVEF; *Evolution*: severely impaired LVEF	Not described	Not described	Not described	1.0/-	11.00	4421	Yes
35	Male	Chest pain, fatigue	Overweight	None	None	None	None	Repolarization abnormalities	Negative	Normal	Not described	Subepicardial late gadolinium enhancement	Not described	Not described	2.88	Not described	No
59	Male	Fever, vomiting, diarrhoea, cough, dyspnea	Hypertension	Not described	Not described	Bilateral ground-glass opacification	None	High voltages; - Diffused Inverted T waves	LV hypertrophy	Normal	Not described	Subepicardial late gadolinium enhancement	Not described	ND/Not described	9.00	Not described	No
54	Female	Chest pressure	Hypertension, hyperlipidemia	None	None	Not described	Not described	Sinus tachycardia, low QRS voltage, diffuse ST and PR elevations, ST depression in aVR	LV hypertrophy, dilated and severely hypokinetic right ventricle	30%	Not described	Not described	Not described	0.0054 /-	7.9	Not described	Yes
51	Male	Fever, cough, dyspnea	Renal and heart transplant	Multifocal bilateral patchy airspace opacities	None	Not described	Not described	New T wave inversion	Normal cardiac allograft function	Normal	Not described	Not described	120	12.9/-	0.016	3212	No
43	Female	Chest pain, dyspnea	None	Subtle bilateral opacities	None	Bilateral patchy ground-glass opacities	Mid-basal LV hypokinesia, normal apical function	Elevated ST in V1-V2, diffuse U waves	Inferior wall hypokinesis	43%	Intense signal	None	Not described	1.8/-	0.135	512	No
8	Male	Fever, cough, weight loss, fatigue	None	Not described	Not described	Bilateral pneumopathies of the inferior lobes, bilateral pleural effusion,	None	Discrete ST elevation in V3	Impaired left ventricular function, small pericardial effusion, mitral insufficiency	21%	Not described	Subepicardial late gadolinium enhancement	1023	7.3/-	0.044	5112	Yes

Table 1. Clinical characteristics of COVID-19 patients with myocarditis (suspected or diagnosed according to European Society of Cardiology.(18)

Abbreviations: LVEF: left ventricle ejection fraction, MRI: magnetic resonance imaging; LV: left ventricle; IL-6: interleukin-6; CRP: C Reactive Protein; PCT: Procalcitonin; Pro-BNP: pro-brain natriuretic peptide; ND: not determinable.

[a] diagnosis of fulminant myocarditis according to Veronesi et al. and Ammirati et al.(13,14)

Figures

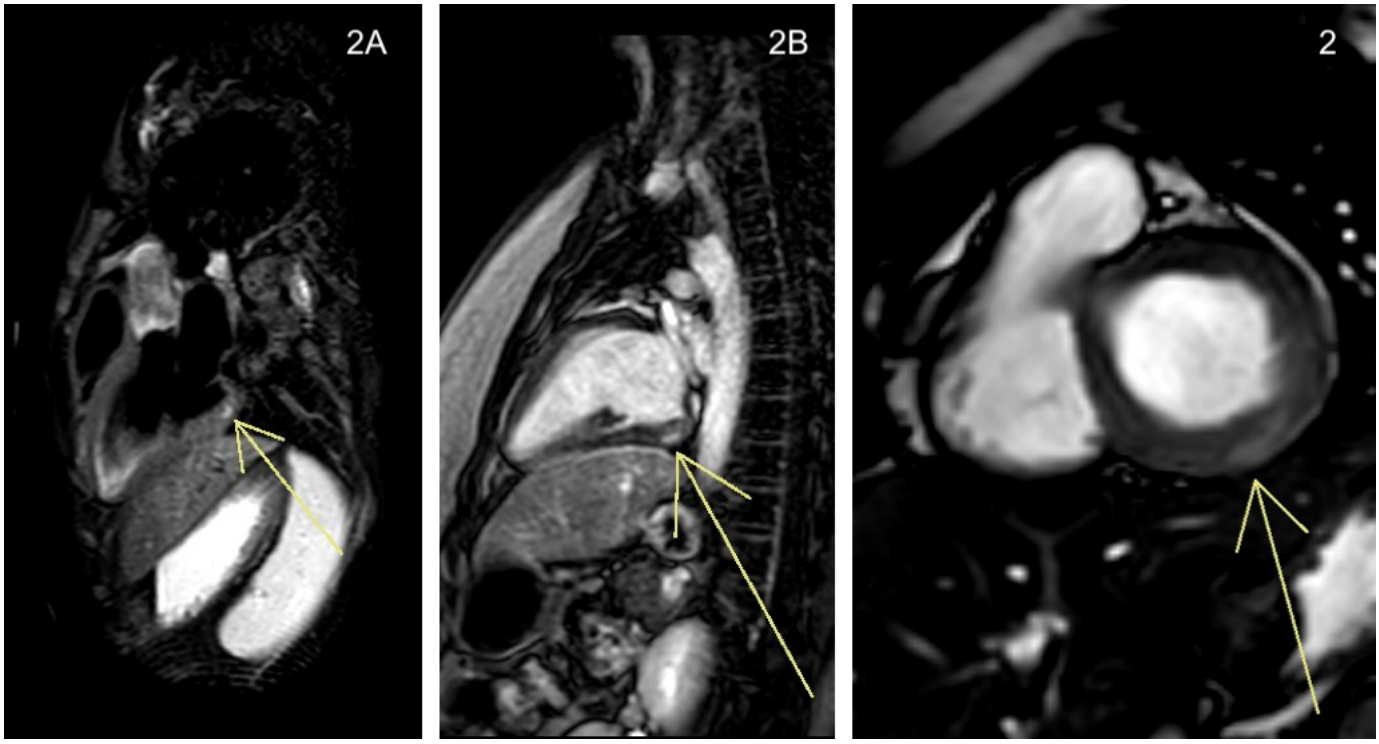

Figure 1

Cardiac MRI showing radiological signs consistent with myocarditis Panel 2A: short tau inversion recovery (STIR) sequences showing a spot of intramyocardial signal hyperintensity (residual edema – yellow arrow); Panel 2B: 3D-two chambers view showing intramyocardial delayed enhancement (subepicardial/“mild-wall”, not ischemic pattern) at inferior basal segment of left ventricle (yellow arrow); Panel 2C: post-contrast image revealing focal delayed enhancement at the same location (yellow arrow)

Figure 2

Course of laboratory inflammation and cardiac necrosis markers and changes in left ventricle ejection rate. Concomitant treatments administered are reported in the panels at the bottom of the picture. Abbreviations: CRP: C Reactive Protein; PCT: Procalcitonin; IL-6: interleukin-6; TnT: troponin T; CPK MB: creatine phosphokinase MB; LVEF: Left Ventricle Ejection Fraction; pro-BNP: pro brain natriuretic peptide; LMWH: low molecular weight heparin.

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