Circulation: Heart Failure

IMAGES AND CASE REPORTS IN HEART FAILURE

Endomyocardial Biopsy in a Pediatric Patient With Cardiac Manifestations of COVID-19

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Although the majority of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exhibit primarily respiratory features, some develop multisystem involvement,[1] which is likely immunologically mediated. Evolving evidence proposes that coronavirus disease 2019 (COVID-19) can present with myocardial injury,[2] with associated increased morbidity and mortality. Several reports describe acute myocarditis[3,4]; however, it remains unclear whether these represent primary viral myocarditis or cytokine-induced myocardial injury,[5] and there is only one published example of SARS-CoV-2 localization within cardiomyocytes on endomyocardial biopsy (EMB).[6] Although initial reports suggested a milder course in children, recent reports of hyperinflammatory shock[7] demonstrate that a mild clinical phenotype is not universal. We present a case exhibiting hyperinflammatory shock and discuss findings of the first reported EMB in a pediatric patient with COVID-19.

CASE REPORT

A 39 kg, 11-year-old girl, with a history of mild asthma, presented with 3 days of fever, myalgia, abdominal pain, and diarrhea. There was evidence of conjunctivitis and cervical lymphadenopathy but no additional stigmata of Kawasaki Disease. Her mother had fever, cough, and anosmia 3 weeks prior. Within 48 hours, despite antibiotics, she developed hemodynamic instability and metabolic acidosis and required multiple inotropes, intubation, and ventilation. She remained acidotic, with blood lactate of 7 mmol/L, and rapidly developed progressive thrombocytopenia (89–50×10^9/L), rising C-reactive protein (CRP; 134–305

mg/L), and marked elevation of both D-dimers (>5000 µg/L) and troponin I (40–2055 ng/L). Echocardiography showed left ventricular (LV) dilatation and severe global systolic dysfunction (LV ejection fraction <20%). Nasopharyngeal aspirate polymerase chain reaction was positive for SARS-CoV-2. She was referred to us for consideration of extracorporeal membrane oxygenation.

On arrival, venoarterial extracorporeal membrane oxygenation was rapidly initiated via the right common carotid artery and right internal jugular vein. She developed extensive bilateral lung consolidation and required norepinephrine and epinephrine infusions to maintain an appropriate blood pressure, although end-organ function was preserved. Her laboratory profile (Figure 1) demonstrated a marked systemic inflammatory response (peak CRP, 321 mg/L, ferritin, 1529 µg/L, D-dimer, 5852 µg/L), and 16s rDNA polymerase chain reaction was negative. She received 2 doses of intravenous immunoglobulin (but not targeted monoclonal antibody), and methylprednisolone was commenced. With a low admission viral load (cT 34.5428) and subsequently serial negative polymerase chain reaction, remdesivir was not advised.

Atrial septostomy was performed for left atrial dilatation, absent aortic ejection, and pulmonary edema, with satisfactory reduction in left atrial pressure. Right ventricular EMB samples were obtained.

Cardiomyopathy screening (including viral panel) was noncontributory; however, vitamin D supplementation was initiated for a level of <7 nmol/L. NT-proBNP (N-terminal pro-B-type natriuretic peptide) was >35 000 pg/mL on admission, and her troponin I was 829 ng/L (Figure 1); both normalized within 11 days.

Key Words: biopsy ■ cardiomyopathy ■ child ■ COVID-19 ■ inflammation

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Histology of the biopsy (Figure 2) showed interstitial edema, increased numbers of lymphocytes and macrophages, and prominent capillary endothelium without intraluminal thrombosis. There were areas of myocyte dropout but no unequivocal evidence of myocyte necrosis, giant cells, or granulomas. CD3 staining (Figure 3) demonstrated increased T-lymphocytes; C4d immunostaining was negative, indicating no complement deposition. Human Leukocyte Antigen - DR isotype (HLA-DR) was not activated. SARS-CoV-2 polymerase chain reaction of the biopsy was negative. The findings were considered borderline for lymphocytic myocarditis.

There was gradual improvement of cardiorespiratory status and resolution of LV dimensions and function (LV internal diameter in diastole 39.1 mm, LV fractional shortening 29%, LV ejection fraction [Biplane] 67%), permitting extracorporeal membrane oxygenation decannulation on day 11. There was no pericardial effusion, and coronary artery parameters remained normal.

All further swabs for SARS-CoV-2 were negative. COVID-19 IgG was positive both at admission and discharge. Ongoing clinical improvement resulted in transfer to her local unit for rehabilitation.

DISCUSSION

Definitive diagnosis of myocarditis remains challenging. Cardiac magnetic resonance cannot reliably distinguish viral from nonviral causes, its therapeutic value is limited, and is restricted by COVID-19 precautions. EMB, the gold standard, is seldom undertaken in children; we performed this without increased risk to staff or patient as septostomy was already clinically indicated. There remain concerns that published histopathologic criteria demonstrate insufficient sensitivity, with resultant false negatives.[8] The described presentation is consistent with clinically suspected myocarditis, although the biopsy alone would not meet criteria for definitive diagnosis.[5] Additionally, viral RNA was not isolated within the cardiomyocytes—consistent with most reports from current adult literature.[4] Only a single case of virus isolation from within cardiomyocytes has been published, contrasting with the 2009 SARS-CoV epidemic, where direct viral injury was well described.[9]

Alternative possible mechanisms to direct viral myocardial injury in SARS-CoV-2 include hypoxia-induced injury, downregulation of angiotensin II–converting enzyme receptors perpetuating the inflammatory response, and cytokine-induced injury resulting from imbalance between innate and adaptive immune responses, as well as pathological amplification of inflammatory factors, such as NF-κB (nuclear factor κB).[10] We postulate here that either steroid therapy attenuated the biopsy features of myocarditis, or this was a predominantly cytokine-driven process, consistent with interstitial edema and prominent capillary endothelium or both. This is the first report of EMB in a child with COVID-19 and cardiac compromise. Further etiological investigation of myocardial involvement may direct therapeutics and impact clinical outcomes.

ARTICLE INFORMATION

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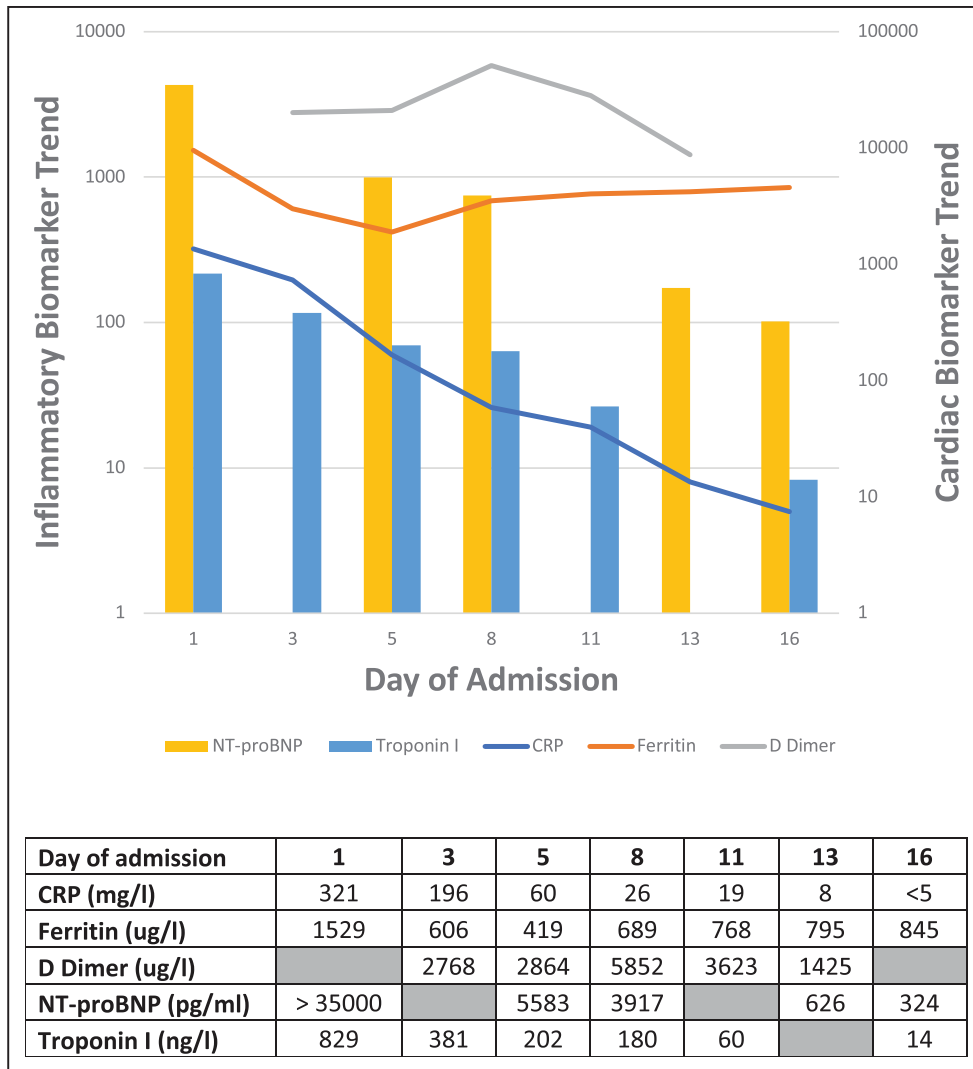
Disclosures

None.

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Day of admission	1	3	5	8	11	13	16
CRP (mg/l)	321	196	60	26	19	8	<5
Ferritin (ug/l)	1529	606	419	689	768	795	845
D Dimer (ug/l)		2768	2864	5852	3623	1425	
NT-proBNP (pg/ml)	> 35000		5583	3917		626	324
Troponin I (ng/l)	829	381	202	180	60		14

Figure 1. Graph demonstrating (log transformed) inflammatory biomarker and cardiac enzyme trends during admission and table below with actual values.
CRP (C-reactive protein; mg/L); Ferritin (µg/L); D-Dimer (µg/L); NT-proBNP (N-terminal pro-B-type natriuretic peptide; pg/mL); troponin I (ng/L).
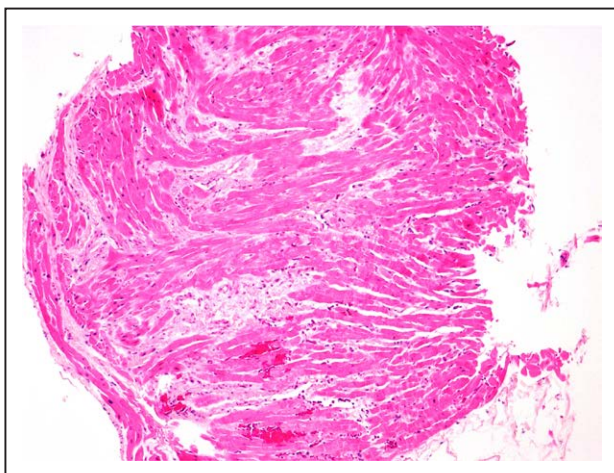
Figure 2. Histological section of endomyocardial biopsy showing an increase in interstitial mononuclear cells, interstitial edema, and areas of myocyte dropout (hemotoxylin and eosin stain, ×10 magnification).
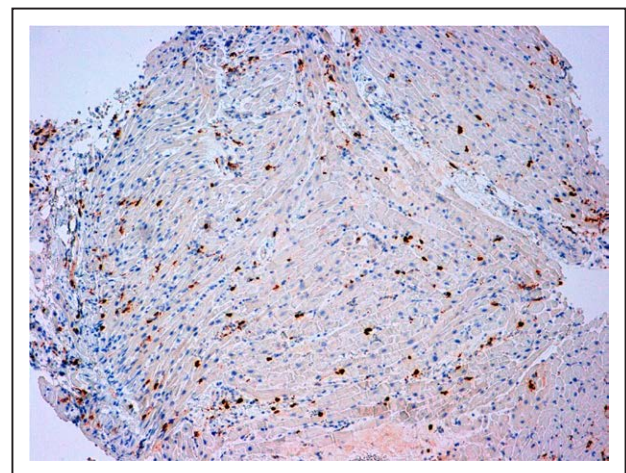
Figure 3. Immunohistochemistry for CD3 highlights increased numbers of lymphocytes within the interstitium.