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

Craig Laurence, MB ChB, MMed; Mohammad Haini, MBBS; Timothy Thiruchelvam, MB ChB, MRCPCH; Graham Derrick, BMedSci, BM, BS, MRCP; Michael Burch, MD; Robert William Michael Yates, MBChB; Jacob Simmonds, MD (Res), MB BCHir, MRCPCH

Although the majority of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exhibit primarily respiratory features, some develop multisystem involvement, which is likely immunologically mediated. Evolving evidence proposes that coronavirus disease 2019 (COVID-19) can present with myocardial injury, with associated increased morbidity and mortality. Several reports describe acute myocarditis; however, it remains unclear whether these represent primary viral myocarditis or cytokine-induced myocardial injury, and there is only one published example of SARS-CoV-2 localization within cardiomyocytes on endomyocardial biopsy (EMB). Although initial reports suggested a milder course in children, recent reports of hyperinflammatory shock 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 intotropes, intubation, and ventilation. She remained acidic, 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
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 decanulation 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 and is restricted by COVID-19 precautions. EMB, the gold standard, is seldom undertaken in children; we performed and is restricted by COVID-19 precautions.

**REFERENCES**

1. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323:1061–1069. doi: 10.1001/jama.2020.1585
2. Deng Q, Hu B, Zhang Y, Wang H, Zhou X, Hu W, Cheng Y, Yan J, Ping H, Zhou Q. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. Int J Cardiol. 2020;311:116–121. doi: 10.1016/j.ijcard.2020.03.087
3. Zeng JH, Liu YX, Yuan J, Wang FX, Wu WB, Li JX, Wang LF, Gao H, Wang Y, Dong CF, et al. First case of COVID-19 complicated with fulminant myocarditis: a case report and insights. Infection. 2020;48:773–777. doi: 10.1007/s15010-020-01424-6
4. Sala S, Peretto G, Gramegna M, Palmisano A, Villatore A, Vignale D, De Cobelli F, Tresoldi M, Cappelletti AM, Basso C, et al. Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. Eur Heart J. 2020;41:1861–1862. doi: 10.1093/eurheartj/ehaa286
5. Peretto G, Sala S, Caffiero ALP. Acute myocardial injury, MINOCA, or myocarditis? Improving characterization of coronavirus-associated myocardial involvement. Eur Heart J. 2020;41:2124–2126. doi: 10.1093/eurheartj/ehaa396
6. Tavazzi G, Pellegrini C, Maurelli M, Bellia M, Scicutti F, Bottazzi A, Sepe PA, Ressasco T, Camorotondo R, Bruno R, et al. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail. 2020;22:911–915. doi: 10.1002/ejhf.1828
7. Belhadjer Z, Muet M, Bajolle F, Khraiche D, Legendre A, Ababka S, Auriau J, Grimaud M, Oulahna M, Beggitti M, et al. Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation. 2020;142:436–436. doi: 10.1161/CIRCULATIONAHA.120.048360
8. Baughman KL. Diagnosis of myocarditis: death of Dallas criteria. Circulation. 2006;113:953–959. doi: 10.1161/CIRCULATIONAHA.105.589663
9. Ouedry Y, Kaissirz Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, Butany J. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest. 2009;39:618–625. doi: 10.1111/j.1365-2362.2009.02153.x
10. Liu PP, Blett A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. Circulation. 2020;142:68–78. doi: 10.1161/CIRCULATIONAHA.120.047549
**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).

| Day of admission | 1  | 3  | 5  | 8  | 11 | 13 | 16 |
|------------------|----|----|----|----|----|----|----|
| CRP (mg/L)       | 321| 196| 60 | 26 | 19 | 8  | <5 |
| Ferritin (µg/L)  | 1529 | 606 | 419 | 689 | 768 | 795 | 845 |
| D Dimer (µg/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 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.