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CASE REPORT

Fulminant myocarditis in a patient with coronavirus disease 2019 and rapid myocardial recovery following treatment

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Abstract

Coronavirus disease 2019 (COVID-19) is a global pandemic increasingly encountered in the clinical setting. It typically manifests as a respiratory illness, although cardiac involvement is common and portends a worse prognosis. We present the case of a 56-year-old male admitted with COVID-19 fulminant myocarditis and cardiogenic shock. We discuss important aspects of the multidisciplinary and interventional care involved in treating cardiogenic shock as well as the likely mechanisms of, and potential treatment for, COVID-19 myocarditis. The various pathways of myocardial injury, including direct viral damage, macrophage activation, and lymphocytic infiltration, are outlined in detail in addition to associated pathology such as cytokine release syndrome. COVID-19 is a complex and multisystem disease process; in addition to supportive care, specific consideration should be given to the underlying mechanism of injury for each patient.

Keywords Myocarditis; Cardiogenic shock; COVID-19; Mechanical support; Echocardiography

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Introduction

Cardiogenic shock is a rare though important clinical entity associated with coronavirus disease 2019 (COVID-19) that requires rapid recognition and multidisciplinary treatment. Putative mechanisms of injury may include fulminant myocarditis (FM), takotsubo cardiomyopathy, severe inflammation with cytokine release syndrome, and direct viral injury with macrophage activation, which are discussed in the succeeding text. Distinguishing between these mechanisms can only be achieved by endomyocardial biopsy (EMBx); however, this is not always practical to perform. If myocardial inflammation is suspected/confirmed, consideration should be given to anti-inflammatory and immunomodulatory therapies, although the effectiveness of such treatment is poorly understood and must be weighed against the risk of potentially prolonging viral persistence. With the appropriate multidisciplinary care, prompt myocardial recovery is possible and demonstrated in the following report.

Case report

A 56-year-old male with a history of obesity (body mass index = 35) and hyperlipidaemia presented to the emergency department with 1 day of dyspnoea and lethargy. He reported close contact with a COVID-19-positive coworker. He was in respiratory distress with measured oxygen saturation (SaO_2) of 66%, hypotensive, and in rapid atrial fibrillation. He rapidly progressed to respiratory failure and shock requiring mechanical ventilation and three vasopressors.

Initial investigation included laboratory studies that were notable for white blood cell count 9.8 K/μL (66% neutrophils and 19% lymphocytes), haemoglobin 19.4 g/dL (declined to 15.2 g/dL after fluid administration), creatinine 2.0 mg/dL, B-type natriuretic peptide 790.0 pg/mL, troponin I 1.3 ng/mL, lactate 8.7 mmol/L, D-dimer 1961 ng/mL, C-reactive protein 4.1 mg/dL, and procalcitonin 1.4 ng/mL with unremarkable liver chemistries. An arterial blood gas (on 100% FiO_2) demonstrated a pH of 7.25 and partial pressure of oxygen (PaO_2) of 319 mmHg; the initial venous haemoglobin saturation drawn from the superior vena cava was 80% (on the same FiO_2). His electrocardiogram (EKG) showed rapid atrial fibrillation and low voltage (*Figure 1A*). Transthoracic echocardiogram (TTE) revealed extreme concentric left ventricular (LV) hypertrophy (LVH) with a wall thickness of 2.0 cm, reduced biventricular function with LV ejection fraction (EF) of 20%, and a small pericardial effusion (Supporting Information, *Video S1A* and *S1B*). A chest X-ray showed multifocal bilateral airspace disease, a general respiratory viral panel was negative, but the rapid Abbott ID NOW™ COVID-19 test resulted positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (later confirmed on the Cepheid Xpert® Xpress testing system).

The clinical presentation of acute respiratory failure with rapidly progressive shock and biventricular dysfunction suggested a diagnosis of COVID-19 FM. The discrepancy between the degree of LVH and low voltage on EKG hinted at significant myocardial oedema, further supporting this diagnosis. After a multidisciplinary discussion, the patient was cannulated on peripheral veno-arterial extracorporeal membrane oxygenation with a distal perfusion catheter. Repeat TTE, on admission to the intensive care unit, revealed an EF $<$ 5%, and his arterial line waveform was non-pulsatile (Supporting Information, *Video S2A* and *S2B*). A femoral Impella 2.5 (Abiomed U.S., Danvers, MA) was inserted for LV venting. The patient was treated with methylprednisolone 100 mg and tocilizumab 800 mg. Because of continued cardiac standstill, his methylprednisolone was readministered at increasing doses (200, 200, and 500 mg) for a total of 4 days. As his inflammatory markers briefly decreased (*Figure 2*), tocilizumab was not re-dosed and no other COVID-19 targeted therapy was administered. Despite initial haemodynamic improvement, he developed oliguric kidney failure requiring continuous venovenous haemofiltration. As a result of retroperitoneal injury and haemorrhage, he was decannulated from VA-EMCO on hospital day (HD) 4 and transitioned to biventricular support with a ProtekDuo (LivaNova, London, UK) and axillary Impella 5.0; transoesophageal echocardiogram completed in the operating room noted improved LV function (EF 50%). TTE on HD 7 revealed further EF recovery to 65% (Supporting Information, *Video S2A* and *S2B*), EKG exhibited return to sinus rhythm (*Figure 1B*), and arterial line tracings showed improved pulsatility; he was ultimately able to be weaned from both Impella (HD 10) and ProtekDuo (HD 12). Interestingly, he then developed severe vasoplegia, requiring high-dose vasopressor support, correlating with increasing markers of inflammation, and myocardial injury. Re-dosing tocilizumab at this time was considered but ultimately deferred because of clinical improvement. As of this writing, the patient has recovered from critical illness and is currently on the general medical floor awaiting discharge to a rehabilitation centre.

Figure 1 (A) Initial 12-lead electrocardiogram and (B) follow-up 12-lead electrocardiogram on Day 12.

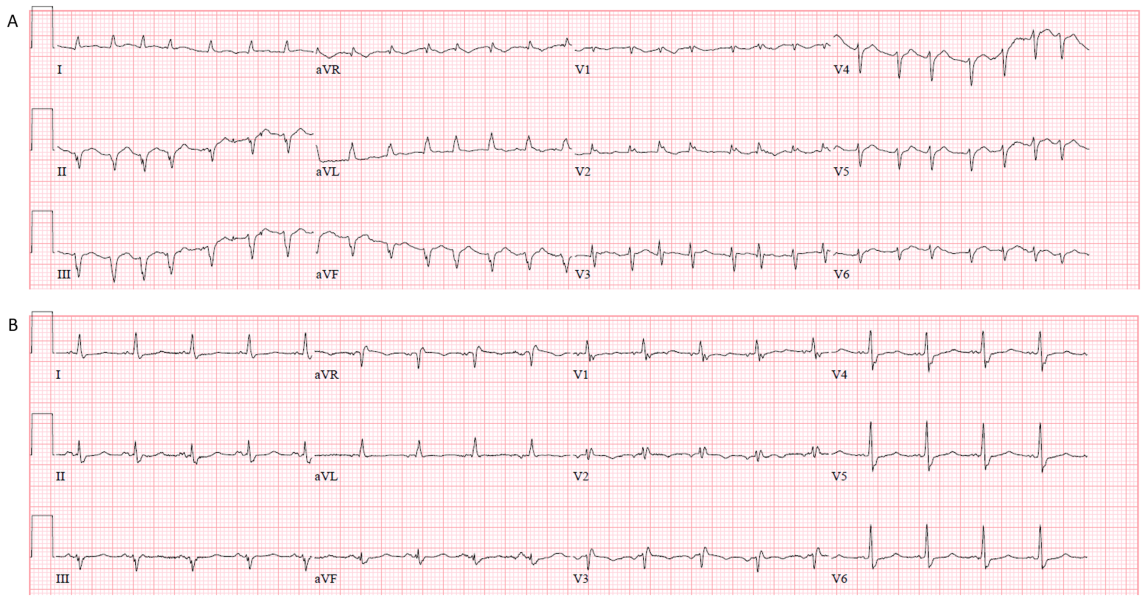

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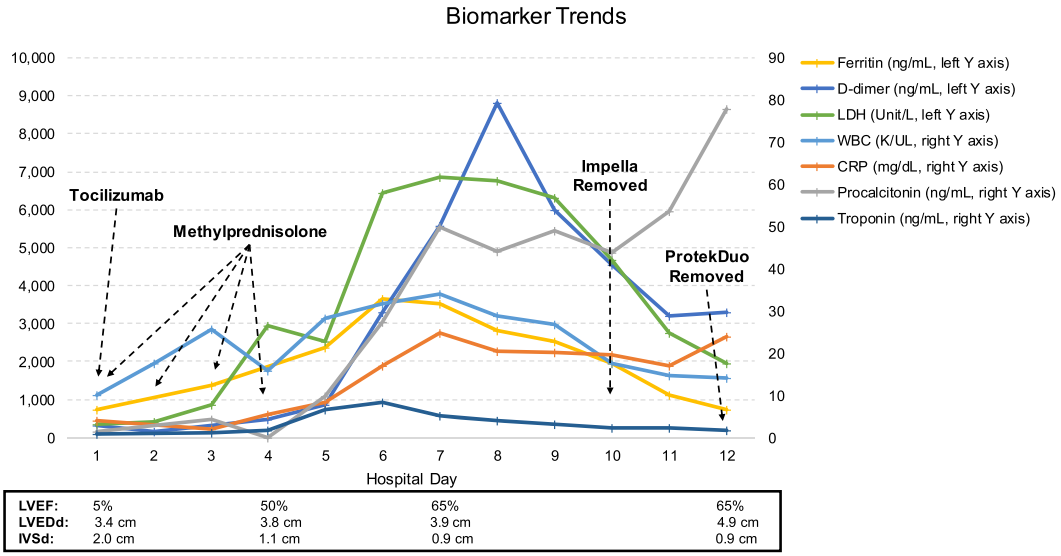
Figure 2 Biomarkers of inflammation and cardiac injury by hospital day. CRP, C-reactive protein; IVSd, interventricular septum thickness in diastole; LDH, lactate dehydrogenase; LVEDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; WBC, white blood cell.



Discussion

We present a case of cardiogenic shock due to presumed FM vs. direct viral damage associated with SARS-CoV-2 infection. Critical illness in COVID-19 is primarily driven by acute respiratory distress syndrome with a concomitant profound hyperinflammatory response. Thus, the majority of myocardial injury seen in COVID-19 is presumed to be the result of 'collateral damage' from the inflammatory response and critical illness. However, a subgroup of individuals develop primary myocardial dysfunction with a clinical picture consistent with acute myocarditis. Proposed mechanisms of direct myocardial injury in COVID-19 include (i) acute myocarditis defined by an amplified lymphocytic immune response as well as (ii) direct viral damage putatively mediated by activated macrophages; each has been shown to play a role in published case reports.[1–4] Distinguishing between these two mechanisms requires EMBx, which is often deferred because of patient acuity and concern for further viral spread.

Our case adds to this nascent but growing literature. An acute presentation, as seen in this case (<1 day of symptoms progressing to shock) suggests the role of direct viral injury to the myocardium triggering an exaggerated innate immune response. Autopsy data from COVID-19 demonstrated direct SARS-CoV-2 infection of extracardiac macrophages and up-regulation of interleukin (IL)-6 within these macrophages, and autopsy data from the SARS-CoV-1 outbreak demonstrated significant macrophage accumulation in the myocardium of affected hearts.[2,3] Acute infiltration of the myocardium with pro-inflammatory macrophages is likely to result in significant cytotoxic damage and secondary oedema, which may have contributed to the LVH and echo-bright appearance seen in this case. EMBx from a similar presentation of refractory shock demonstrated prominent macrophages containing SARS-CoV-2 viral inclusions with noticeable paucity of inflammation and necrosis, further supporting the mechanism of direct viral damage mediated by activated macrophages.[4] The low troponin level seen at presentation as well as rapid recovery is further consistent with this mechanism of macrophage injury and resultant oedema rather than necrosis. A report by Sala *et al*. demonstrated contradictory histological findings of lymphocytic infiltration, although the clinical presentation differed significantly with only mild myocardial dysfunction (EF 40%) and no haemodynamic instability.[5] Our case is consistent with prior reports demonstrating very rapid resolution of systolic dysfunction and regression of LVH and/or LV dilatation, although none have demonstrated the degree of either myocardial depression or LVH (2 cm) seen in our case.

In contrast to a typical COVID-19 patient presenting with pulmonary manifestations of severe disease, our patient presented with initially low levels of inflammatory and cardiac biomarkers though significant myocardial dysfunction. The patient's subsequent rise in these biomarkers occurred after myocardial recovery and likely signified a second, cytokine predominant, vasoplegic stage of disease. Our patient's trajectory is thus consistent with the stages proposed by Siddiqi and Mehra, albeit with 'the viral response' stages (I and II) manifesting as cardiac compromise rather than pulmonary disease.[6] While it is hard to know how much of the

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improvement in myocardial function can be attributed to tocilizumab, an immunomodulatory therapy targeting the IL-6 pathway does have physiological merit given the underlying hypothesis of pro-inflammatory macrophages promoting myocardial damage and persistent inflammation. Immunomodulatory therapy targeting IL-1, such as anakinra, may also be considered although this remains untested.[7] When encountering similar patients in clinical practice, if inflammatory damage is consistent with the presenting syndrome, serious consideration should be given to anti-inflammatory therapy, such as steroids or other immunomodulatory medications.

Conflict of interest

The authors have no business or financial relationships to disclose, which would in any way bias our work or reporting of this case report.

Author contributions

H.C.G., A.S., and E.E.V. were responsible for preparing the initial draft of the manuscript. All authors shared equally in the editing and preparation of subsequent drafts.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Video S1 (A and B). Echocardiogram on admission, showing (A) parasternal long and (B) parasternal short axis views.

Video S2 *(A and B). First echocardiogram on admission to the intensive care unit, showing (A) apical four chamber and (B) parasternal short axis views.*

Video S3 *(A and B). Follow-up echocardiogram on HD7 showing (A) apical four chamber and (B) parasternal short axis views.*

References

1. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, Mehra MR, Schuepbach RA, Ruschitzka F, Moch H. Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; **395**: 1417–1418.
2. Oudit GY, Kassiri 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.
3. Chen Y, Feng Z, Diao B, Wang R, Wang G, Wang C, Tan Y, Liu L, Wang C, Liu Y, Liu Y, Yuan Z, Ren L, Wu Y. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) directly decimates human spleens and lymph nodes. *medRxiv* 2020. https://doi.org/10.1101/2020.03.27.20045427
4. Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, Sepe PA, Resasco T, Camporotondo R, Bruno R, Baldanti F,Paolucci S, Pelenghi S, Iotti GA, Mojoli F, Arbustini E. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. *Eur J Heart Fail* 2020; **22**: 911–915.
5. Sala S, Peretto G, Gramegna M, Palmisano A, Villatore A, Vignale D, de Cobelli F, Tresoldi M, Cappelletti AM, Basso C, Godino C, Esposito A. 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.
6. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical–therapeutic staging proposal. *J Heart Lung Transplant* 2020; **39**: 405–407.
7. Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, Cron RQ, Opal SM. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase III trial. *Crit Care Med* 2016; **44**: 275–281.