ESC European Society of Cardiology

European Heart Journal - Case Reports
doi:10.1093/ehjcr/ytaa519

CASE REPORT
Other

A case report on transient cardiomyopathy with cytokine storm in SARS-CoV-2

Tushar Tarun [1,3]*, Senthil Kumar[1,3], Jeremy Johnson[2], and Anand Chockalingam[1,3]

[1]Division of Cardiovascular Medicine, University of Missouri—Columbia, 1 hospital Drive, CE 306, Columbia, MO 65201, USA; [2]Division of Pulmonary and Critical Care, Harry S. Truman Memorial Veterans' Hospital, Columbia, MO, USA; and [3]Division of Cardiovascular Medicine, Harry S. Truman Memorial Veterans' Hospital, Columbia, MO, USA

Received 9 June 2020; first decision 2 July 2020; accepted 25 November 2020

Background Cardiac manifestations during Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) pandemic have included acute coronary syndrome, arrhythmias, myocarditis, and stress cardiomyopathy. However, the combination of cardiomyopathy and negative cardiac biomarkers has not yet been reported.

Case summary A 49-year-old man admitted for respiratory failure secondary to SARS-CoV-2 developed new-onset cardiomyopathy with negative cardiac biomarkers. Left ventricular ejection fraction and strain improved 7 days after the initial echocardiogram, after administration of Tocilizumab, coinciding with clinical recovery, and improvement in inflammatory markers.

Discussion As experience of cardiovascular manifestations of SARS-CoV-2 increases, more patients will likely present with cardiovascular manifestations; the recognition and proper management of these may improve patient outcomes.

Keywords SARS-CoV-2 (COVID 19) • Cardiomyopathy • Cytokine storm • Case report

Learning points

- Use of echocardiography with strain helps identify cardiomyopathy in critically ill Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) patients with arrhythmias and negative cardiac biomarkers.
- As the management of SARS-CoV-2 evolves, trend of inflammatory markers may be a surrogate for improvement of cardiomyopathy.

Introduction

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) global pandemic poses a great challenge and threat to the health of the entire world population by causing a systemic illness affecting multiple organ systems. By 8 November 2020, 50.2 million cases of infection were reported worldwide with close to 1.2 million deaths across 190 countries.[1]

Cardiac manifestations with SARS-CoV-2 infection have included acute coronary syndrome, arrhythmias, myocarditis, and stress

* Corresponding author. Tel: 573-882-7272, Fax: 573-884-7743, Email: tarunt@health.missouri.edu
Handling Editor: Matteo Cameli
Peer-reviewers: Rami Riziq Yousef Abumuaileq and Suzan Hatipoglu
Compliance Editor: Max Sayers
Supplementary Material Editor: Ross Thomson

cardiomyopathy.[2] The pathophysiology of cardiac involvement in SARS-CoV-2 is not yet fully understood and may be caused by direct myocardial involvement mediated by acetyl cholinesterase 2, cytokine storm, or hypercoagulable state causing ischaemic injury.[3] Patients with evidence of myocardial injury have shown increased mortality, even without underlying cardiovascular disease.[3,4] We present a case of SARS-CoV-2 cardiomyopathy, where the patient presented with respiratory failure and arrhythmias in the absence of elevated troponin and BNP.

Timeline

4/12/2020	Patient initially presented for diarrhoea, nausea, vomiting, and fever, discharged home after IV fluids, and pending COVID-19 test.
4/13/2020	Patient presented again to the ER, now with higher temperature, shortness of breath, new oxygen requirement after testing positive for COVID-19, admitted to intensive care unit on nasal cannula.
4/14/2020	Patient started on hydroxychloroquine for 5 days, with continued worsening of symptoms and requiring bilevel positive airway pressure to keep saturation above 90%.
4/19/2020	Patient intubated, volume control with tidal volume of 7 mL/kg, positive end-expiratory pressure (PEEP) of 15 cm of H_2O and plateau pressure of 27–30 cm H_2O.
4/20/2020	Echocardiogram shows global hypokinesis, EF 37%, patient given a dose of 400 mg i.v. of tocilizumab, supportive care continued.
4/27/2020	Repeat echo performed showed significantly improved EF of 50% and global longitudinal strain. Patient's PEEP requirement significantly improved, passed spontaneous breathing trial, and later extubated
5/2/2020	Patient eventually discharged home with close follow-up.

Case presentation

A 49-year-old man with a history of type 2 diabetes mellitus (HbA1c 11.1, 1 month prior), untreated hypertension (baseline systolic blood pressure 130–145 mmHg), hyperlipidaemia, morbid obesity (BMI 42 kg/m^2), and obstructive sleep apnoea presented with diarrhoea, nausea, vomiting, low-grade fever (37.2°C), and chills of 4 days duration. He denied shortness of breath, chest pain, or cough. On presentation, he was tachycardiac with a pulse of 102 beats per minute (b.p.m.) but with otherwise normal vital signs and unremarkable physical examination. His chest X-ray (CXR) showed mild pulmonary congestion. He was tested for SARS-CoV-2 and was discharged home after intravenous fluid administration. One day later, he was admitted with a worsening fever of 39.5°C, diarrhoea, dyspnoea, and severe bouts of coughing. His SARS-CoV-2 test was positive. Physical examination was significant for tachypnoea (26 breaths per minute), tachycardia (108 b.p.m.), and coarse breath sounds bilaterally. Cardiac examination revealed normal heart sounds without murmurs. Repeat CXR showed patchy alveolar opacities, superimposed on mild diffuse interstitial opacities.

His Initial laboratory assessment including inflammatory markers was significant for white blood cell count of 5.8 $\times$ 10^3/μL (normal range 3.6–11.20 $\times$ 10^3/μL), 0.6 $\times$ 10^3/μL lymphocytes (normal range 0.77–4.50 $\times$ 10^3/μL), C-reactive protein (CRP) of 9.79 mg/dL (normal range 0–0.5 mg/dL), lactate dehydrogenase (LDH) of 296 U/L (normal range 125–243 U/L), ferritin of 482 ng/dL (normal range 22–275 ng/dL), interleukin 6 (IL-6) of 83.75 pg/mL (normal range <5 pg/mL), D-dimer of <150 μg/L (normal range 0–150 μg/L), troponin I of 0.018 ng/mL (normal range 0–0.033 ng/mL), and BNP of 25 pg/mL (normal range 0–100 pg/mL). His arterial blood gas (ABG) showed a pH of 7.38 with a pO_2 of 66.2 mmHg (normal 75–100 mmHg) and pCo2 of 38.5 mmHg (normal 38–42 mmHg). Electrocardiogram on the day of presentation showed normal sinus rhythm with a rate of 78 b.p.m. without significant abnormalities.

Intervention

He was admitted to the intensive care unit, due to tachypnoea, use of accessory respiratory muscles and respiratory failure (on 2 L of oxygen to maintain oxygen saturation above 90%). He continued to be febrile (up to 39.4°C), and cardiac monitoring demonstrated premature ventricular complexes with ventricular bigeminy (*Figure 1*). On Day 2 of admission, bilevel positive airway pressure (BiPAP) ventilation was initiated intermittently for maintenance of oxygen saturations above 90% and to decrease the work of breathing. He was treated with hydroxychloroquine (400 mg BID for the first day and then 400 mg daily for the next 4 days). QTc interval remained below 460 ms, blood sugar remained elevated but stable between 160 and 200 mg/dL, not requiring insulin. Despite treatment, inflammatory markers and CXR worsened with a progressive decline in patient's respiratory status on BiPAP and requiring intubation on the 6th day. His ABG prior to intubation was significant for severe hypoxaemia with a pO_2 of 60 mmHg (normal 75–100 mmHg) on BiPAP with 60% FiO_2 (fraction of inspired oxygen), pH of 7.36, and pCO_2 of 48 mmHg (normal: 38–42 mmHg). In the initial week of admission, he had multiple episodes of ventricular bigeminy typically lasting for 30 min to an hour every 4–6 h. Echocardiogram performed on Day 7 for clinical deterioration and arrhythmia showed global hypokinesis, left ventricular ejection fraction (LVEF) of 37% by Simpson's biplane method (*Figure 2A and B*, Supplementary material online, *Videos S1* and *S2*) and markedly abnormal global longitudinal strain, an average of –1% (*Figure 3A*). The end-diastolic volume (EDV) calculated on the apical four-chamber was 131 mL and end-systolic volume (ESV) was 80.7 mL (normal EDV is 62–150, ESV is 21–61 mL). Cardiac function previously was normal (LVEF 60–65%) on an echocardiogram 2 months earlier.

The differential for this new diagnosis of cardiomyopathy included arrhythmia associated, acute viral myocarditis, and stress cardiomyopathy in the setting of cytokine storm. His troponin I continued to be negative at 0.019 ng/mL (normal 0–0.033 ng/mL), BNP remained low at 13 pg/mL (normal 0–100 pg/mL). Given clinical

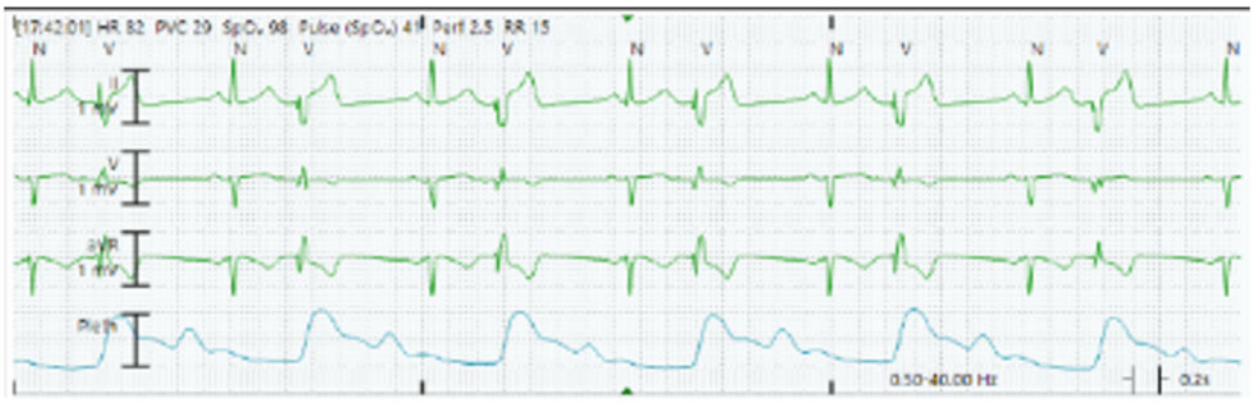

Figure 1 Telemetry strip showing Ventricular bigeminy.

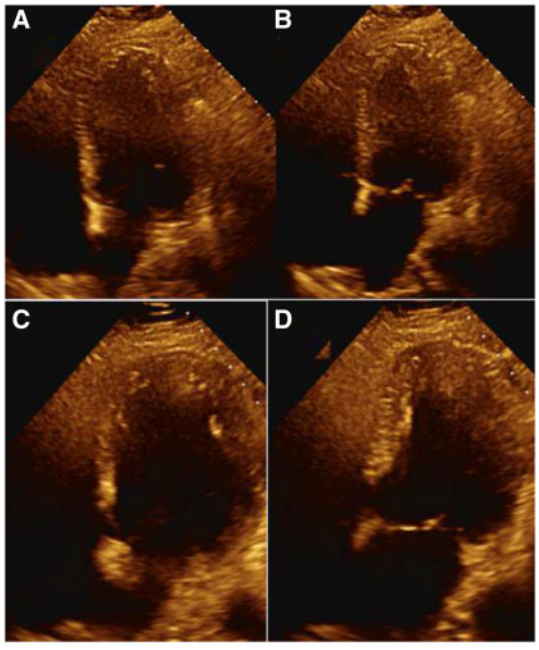

Figure 2 (*A*) and (*B*) End-diastolic and end-systolic frames during the first echo. (*C*) and (*D*) End-diastolic and end-systolic frames during repeat echo.

decompensation and worsening IL-6 levels (243 pg/mL), a single 400 mg dose of tocilizumab (TCZ) was administered on Day 7. With supportive care, he showed a gradual improvement in respiratory status and ventilatory requirements. He was initially on volume control with a tidal volume of 7 mL/kg, positive end-expiratory pressure (PEEP) of 15 cm of H_2O, and plateau pressure of 27–30 cm H_2O. His PEEP continued to decrease on the ventilator along with improvement in ventilator mechanics. On Day 14, a repeat echocardiogram showed improved LVEF of 50% (*Figure 2C* and *D*, Supplementary material online, *Videos S3* and *S4*), with significant improvement in global longitudinal strain of -12% (*Figure 3B*). His EDV was 125 mL and ESV was 77 mL. He was extubated the same day after passing a spontaneous breathing trial and continued to improve clinically. Inflammatory markers demonstrated marked improvement (trends of interleukin-6 and CRP have been shown in *Figures 4* and *5*), with improvement in clinical symptoms after administration of TCZ. The patient was later discharged home on no supplemental oxygen, followed up in the clinic in 2 weeks, with no acute complaints. On exam, he was euvolemic. His repeat electrocardiogram showed normal sinus rhythm with no arrhythmias. Since he had improved with no new complaints, no further cardiac testing was carried out.

Discussion

This case of respiratory failure, arrhythmias, and cardiomyopathy, had normal cardiac biomarkers with normal troponin I and BNP levels. There was a significant elevation of IL-6 levels (up to 1387 pg/mL; normal < 5 pg/mL), which improved with a single dose of TCZ (IL-6 inhibitor), accompanied with clinical improvement and decline in inflammatory markers. This report is the first case of SARS-CoV-2 cardiomyopathy and significant systolic dysfunction without biomarker evidence of myocardial injury. Although this patient's BNP and troponin I did not increase, his transient cardiomyopathy was likely a case of global stress cardiomyopathy in the setting of cytokine storm. The time period of significant improvement in ejection fraction and strain after a week fits the expected time course of stress cardiomyopathy. Given that he did not have any arrhythmias prior to admission and also during his initial visit to the emergency room it made it less likely to be arrhythmia associated. In the setting of normal troponin I and BNP through the course, viral myocarditis was also a less likely aetiology. Due to the acuteness of the presentation and the critical nature of the illness, cardiac magnetic resonance imaging (MRI) was not performed which would have helped in characterization of the myocardium and better understand the underlying pathology.

Stress cardiomyopathy is now a widely recognized entity, especially in the setting of physical and emotional stress, and it does appear that cytokine storm induces a significant physical stress. There are more reports of stress cardiomyopathy with SARS-CoV-2, with one

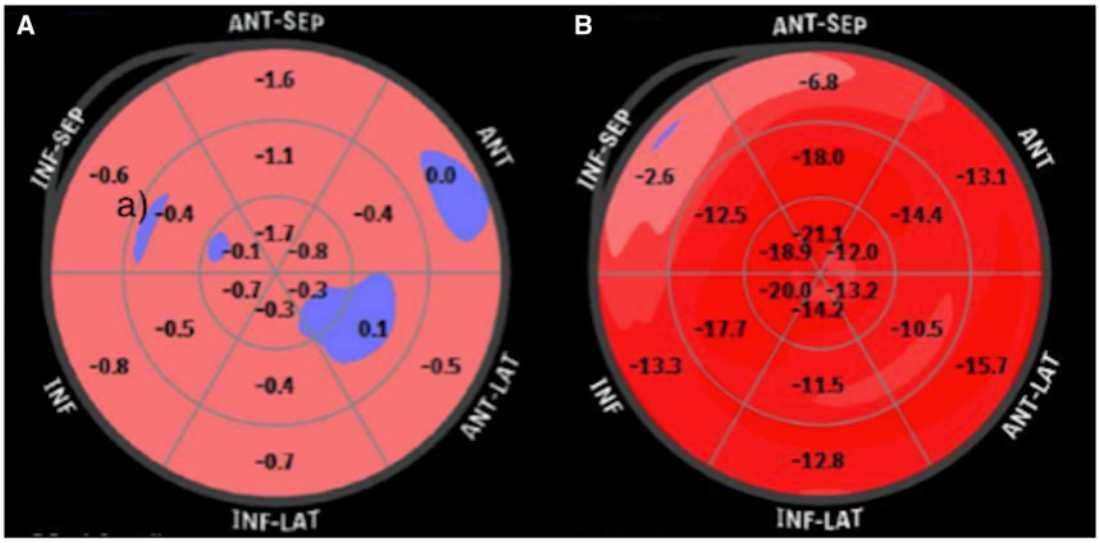

Figure 3 (*A*) Bull's eye plot during initial echocardiogram showing severely decreased global longitudinal strain. (*B*) Bull's eye plot of repeat echocardiogram showing improved strain.

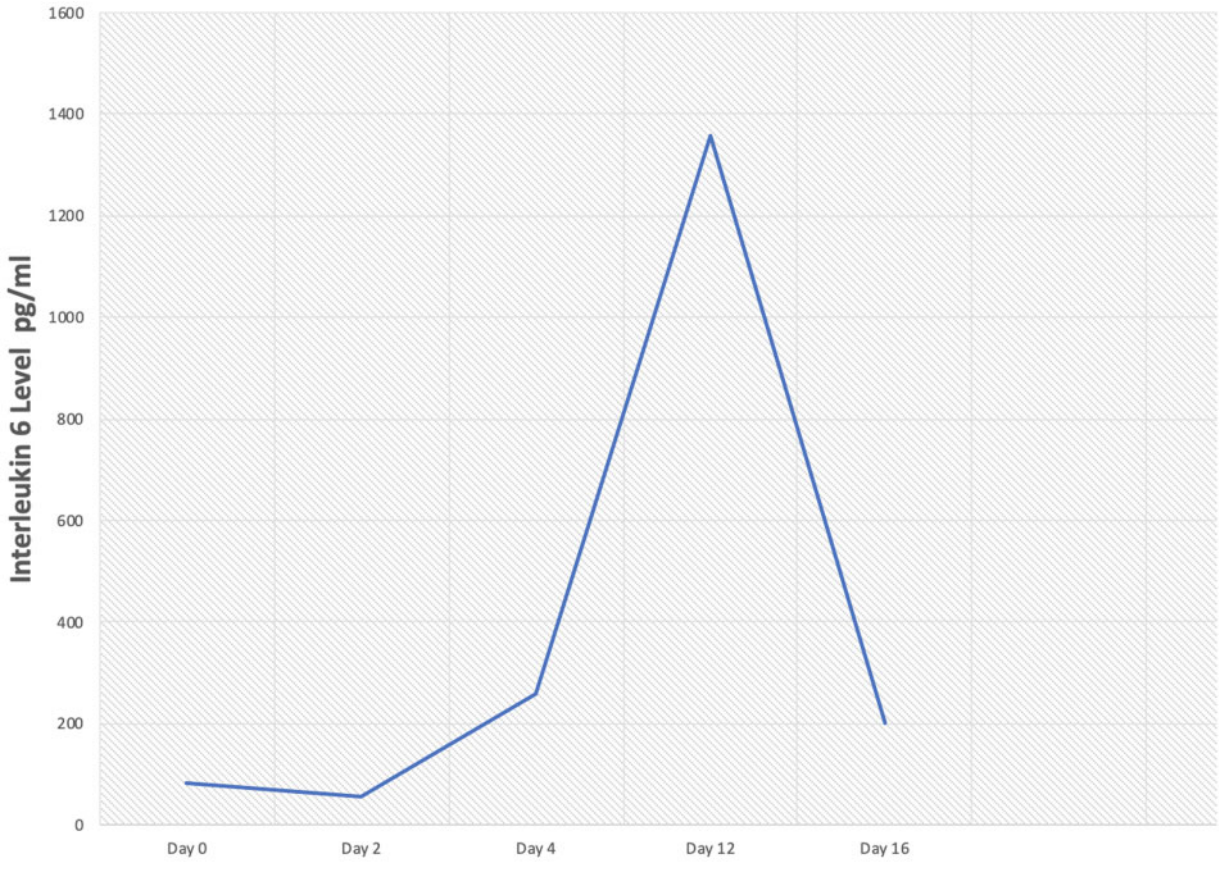

Figure 4 Trend of IL-6, showing initial rise of the IL-6 level (on Y-axis) then taper down with days of hospitalization (X-axis).

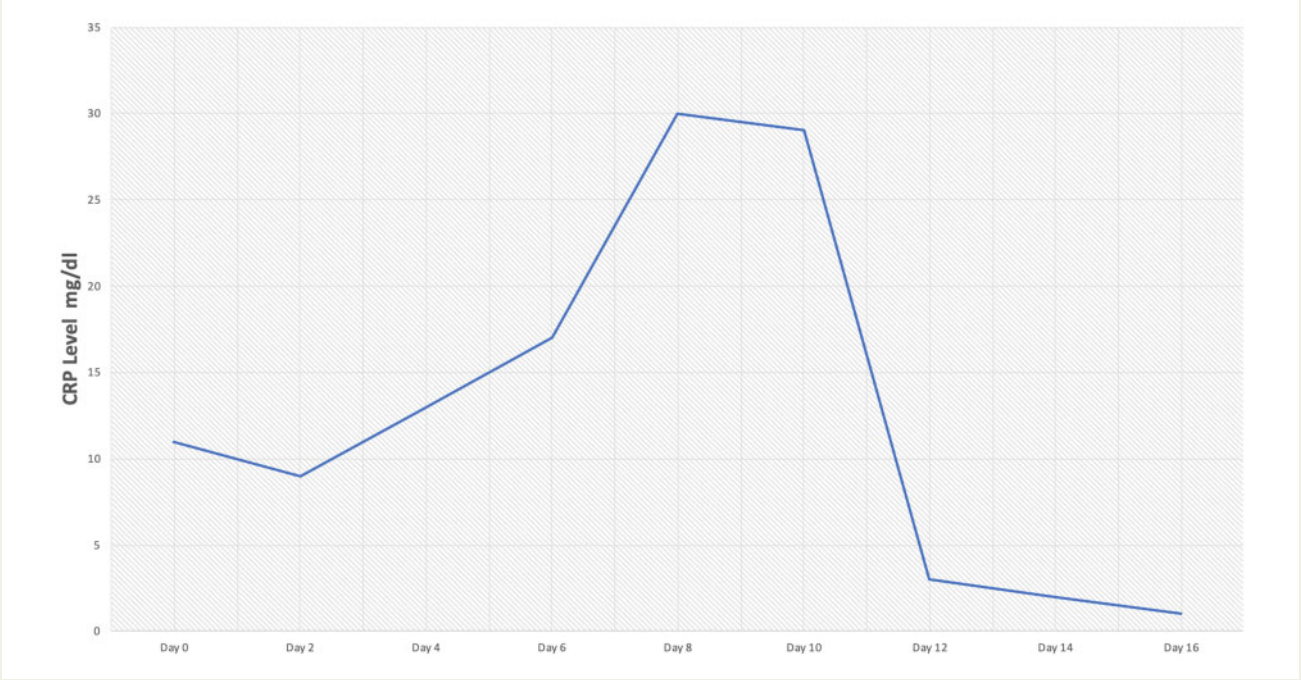

Figure 5 Trend of C-reactive protein, showing initial rise of the C-reactive protein level (Y-axis) and then taper down with days of hospitalization (X-axis).

systematic review of different case reports suggesting that cytokine storm is likely to play a role in the development of stress.[5] The other aetiology of cardiac involvement also includes direct myocardial involvement with SARS-CoV-2 infection as seen in a prospective study from Germany which showed myocardial inflammation in 60% of MRI studies in patients recovered from SARS-CoV-2.[6]

At this time multiple therapeutic options in SARS-CoV-2 are being evaluated, one of which is Tocilizumab (TCZ) which was used in our patient. TCZ is an IL-6 inhibitor that is approved for use in patients receiving chimeric antigen receptor T-cell (CAR-T) therapy who experience severe cytokine release syndrome and who typically present with high fever, vasodilatory shock, and severe elevation of inflammatory markers such as LDH, CRP, and IL-6.[7] SARS-CoV-2 with cytokine storm can progress in a similar manner. Even though randomized controlled trials are ongoing on the use of TCZ in SARS-CoV-2 patients at this time, retrospective studies and case reports suggest its utility in patients with severe cytokine storm.[8] Tocilizumab may be an important treatment modality in patients with cardiac decompensation and cytokine storm. The preliminary results of the COVACTA trial have shown no benefit in mortality but decrease in length of hospital stay with the use of TCZ in SARS-CoV-2. The complete results of RECOVERY trial with the use of TCZ are still awaited, although the preliminary data did not show any mortality benefit.[9] There are other agents undergoing clinical trials, some of which include convalescent plasma, interferon, lopinavir/ritonavir, Favipiravir, dexamethasone, and remdesivir,[10] of which dexamethasone and remdesivir have shown evidence of clinical benefit. The ACCT-1 study, on remdesivir has shown superiority to placebo in shortening the time to recovery in adults who were hospitalized with SARS-CoV-2 and had evidence of lower respiratory tract infection.[10]

The RECOVERY trial on the use of dexamethasone has also shown a 28-day mortality benefit in patients who are on mechanical ventilation or supplemental oxygen.[11] Although the clinical trials are now presenting more robust data regarding the role of different therapies with regards to mortality, much work still needs to be done regarding the recognition of incidence and treatment of new-onset cardiomyopathy in the setting of SARS-CoV-2 infection.

Conclusion

As experience of cardiovascular manifestations of SARS-CoV-2 increases, more patients will likely present with cytokine storm and cardiac dysfunction manifesting in the form of cardiomyopathy, arrhythmias, or myocardial injury. The outcome of the patient may depend on the recognition and proper management of these cardiovascular manifestations.

Lead author biography

Dr. Tarun is a third year Cardiolovascular Medicine fellow in training at University of Missouri-Columbia. His interests are cardiovascular imaging and cardio-oncology.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: Consent was obtained from the patient and permission obtained from the privacy officer at the Veterans Administration hospital, in Columbia MO.

Conflict of interest: none declared.

Funding: none declared.

References

1. COVID-19 Dashboard by the Center for Systems Science Engineering (CSSE) at Johns Hopkins University. JHU. https://coronavirus.jhu.edu/map.html (24 May 2020).
2. Kang Y, Chen T, Mui D, Ferrari V, Jagasia D, Scherrer-Crosbie M *et al.* Cardiovascular manifestations and treatment considerations in covid-19. *Heart* 2020;**106**:1132–1141.
3. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F *et al.* Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020;**5**:802.
4. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T *et al.* Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;**5**:811.
5. Singh S, Desai R, Gandhi Z, Fong HK, Doreswamy S, Desai V *et al.* Takotsubo syndrome in patients with COVID-19: a systematic review of published cases. *SN Compr Clin Med* 2020;doi: 10.1007/s42399-020-00557-w..
6. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J *et al.* Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;**5**:1265.
7. Frey N, Porter D. Cytokine release syndrome with chimeric antigen receptor T cell therapy. *Biol Blood Marrow Transplant* 2019;**25**:e123–e127.
8. Xu X, Han M, Li T, Sun W, Wang D, Fu B *et al.* Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA* 2020;**117**: 10970–10975.
9. Furlow, B. COVACTA trial raises questions about tocilizumab's benefit in COVID-19. *Lancet* 2020;**2**:E592.
10. Robinson J. The Pharmaceutical Journal, *PJ June* 2020 online; doi: 10.1211/PJ.2020.20208126.
11. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC *et al.* Remdesivir for the treatment of Covid-19—final report. *N Engl J Med* 2020;**383**: 1813–1826.
12. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, *et al.* RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. *N Engl J Med* 2020;doi: 10.1056/NEJMoa2021436.