Successful treatment of acute heart failure in COVID-19-induced cytokine storm with tocilizumab: a case report

Kalyan R. Chitturi 1*, Sameer Thacker1, Mukhtar A. Al-Saadi1, and Mahwash Kassi2

1Department of Medicine, Houston Methodist Hospital, Houston, TX, USA; and 2Department of Cardiology, Houston Methodist DeBakey Heart & Vascular Center, Houston, TX, USA

Received 22 April 2020; first decision 27 April 2020; accepted 2 June 2020; online publish-ahead-of-print 17 July 2020

Background
SARS-CoV-2 is known to induce a cytokine storm, a hyperinflammatory state driven by up-regulation of interleukin 6 (IL-6) and immunomodulatory chemokines that may result in acute heart failure.

Case summary
A 65-year-old woman with confirmed SARS-CoV-2 developed shock with multiorgan system failure, including acute biventricular heart failure, 2 weeks after the initial onset of fever, cough, and shortness of breath. The patient experienced myocardial recovery within 48 h after administration of tocilizumab, a humanized monoclonal anti-IL-6 receptor antibody, and multiple supportive vasoactive medications.

Discussion
The differential diagnosis of acute heart failure in critically ill patients with COVID-19 infection is broad, including sepsis-induced cardiomyopathy, Takotsubo syndrome, viral lymphocytic myocarditis, and acute coronary syndrome. Immunomodulatory treatment with tocilizumab may benefit patients who develop cardiogenic shock associated with SARS-CoV-2-induced cytokine storm.

Introduction
Cytokine storm, the abrupt onset of systemic hyperinflammation in the most critically ill patients infected by SARS-CoV-2, is associated with high mortality. The pathophysiology of SARS-CoV-2-induced cytokine storm involves high expression of interleukin-6 (IL-6), which activates hepatocyte synthesis of acute-phase reactants. A cardio-protective proinflammatory cytokine in the acute setting, IL-6 stimulates immune cells to prevent myocardial injury from oxidative stress and apoptosis, though marked increases result in dysregulation. Tocilizumab, a humanized monoclonal antibody against IL-6, may be an effective treatment of acute heart failure in patients with SARS-CoV-2-induced cytokine storm.
Timeline

| Date       | Events                                                                 |
|------------|------------------------------------------------------------------------|
| 28 March 2020 | Patient with a history of obesity, type 2 diabetes mellitus, hypertension, hyperlipidaemia, and transient ischaemic attack presented with progressively worsening fever, dry cough, and exertional dyspnoea over a 1-week timespan |
| 31 March 2020 | Patient is advised by her general practitioner to go to the hospital emergency room after she is found to be hypoxic during a clinic visit. Chest imaging revealed bilateral lung ground-glass opacities. Nasopharyngeal swab COVID-19 PCR testing returned positive for SARS-CoV-2. |
| 1 April 2020 | Patient is enrolled in US Clinical Trial NCT04292899 Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734) in Participants with Severe Coronavirus Disease (COVID-19), receiving 7 out of 10 doses of the medication. Patient also received an empiric 7-day course of ceftriaxone and azithromycin for community-acquired pneumonia. |
| 7 April 2020 | Patient decompensated with shock and multiorgan system failure, including acute heart failure, necessitating emergent rapid sequence intubation and transfer to the medical intensive care unit. Transthoracic echocardiography (TTE) showed severe biventricular failure with a left ventricular ejection fraction (LVEF) of 25%. |
| 8 April 2020 | Patient received a 400 mg i.v. dose of tocilizumab in addition to supportive vasoactive medications for shock related to cytokine storm |
| 10 April 2020 | Patient experiences significant clinical improvement. TTE demonstrated myocardial recovery with LVEF of 64% |

Case presentation

A 65-year-old woman presented to the emergency room for evaluation of progressively worsening fever, cough, and shortness of breath over 1 week. Her past medical history was notable for obesity, type 2 diabetes mellitus, hypertension, hyperlipidaemia, transient ischaemic attack, and left-sided breast cancer in remission after mastectomy and adjuvant docetaxel and cyclophosphamide. She was seen by her general practitioner earlier the same day and recommended to go to the hospital after being found to be hypoxic with an oxygen saturation of 87% on room air. A chest computed tomography (CT) 1 day previously demonstrated bilateral ground-glass opacities. Medications on admission included: aspirin 81 mg daily, losartan-hydrochlorothiazide 50–12.5 mg daily, simvastatin 80 mg nightly, levothyroxine 100 μg daily, omeprazole 40 mg daily, metformin 500 mg twice daily, and liraglutide 1.8 mg daily injection.

On admission, she had a temperature of 36.1°C, blood pressure 107/62 mmHg, and heart rate 83 b.p.m. Physical exam revealed diminished breath sounds at lung bases. Chest X-ray demonstrated bilateral infiltrates suggestive of pneumonitis. Nasopharyngeal swab confirmed SARS-CoV-2 positivity. The patient was admitted to a specialized COVID-19 unit and initiated on treatment with remdesivir per clinical trial and empiric antibiotics for community-acquired pneumonia.

On the seventh day of hospitalization (2 weeks after initial symptom onset), the patient rapidly deteriorated into multisystem organ failure, comprising severe acidosis. Propofol, fentanyl, and sodium bicarbonate were used for inotropy, and inhaled epoprostenol facilitated RV unloading, Norepinephrine, vasopressin, and hydrocortisone were used for shock.

The differential diagnosis of new-onset acute biventricular heart failure included sepsis-induced cardiomyopathy, Takotsubo syndrome, viral lymphocytic myocarditis, and acute coronary syndrome. Though beneficial for further differentiation of shock, a Swan–Ganz catheter was not placed for invasive haemodynamic assessment due to clinical instability, and the risk of exposing healthcare personnel to infection. Due to haemodynamic instability and an acute kidney injury, cardiac catheterization or ECG-gated CT angiography for evaluation of coronary artery disease or pulmonary embolism was not feasible. Cardiac magnetic resonance (CMR) or endomyocardial biopsy (EMB) for further tissue characterization was also not possible for similar reasons.

The patient was treated with norepinephrine, vasopressin, dobutamine, sodium bicarbonate, inhaled epoprostenol, hydrocortisone, and a 400 mg dose of tocilizumab. Tocilizumab, a humanized monoclonal antibody against soluble and transmembrane IL-6 receptor, was provided for SARS-CoV-2-associated cytokine storm. Norepinephrine, vasopressin, and hydrocortisone were used for distributive shock refractory to fluid resuscitation. Dobutamine was used for inotropy, and inhaled epoprostenol facilitated RV unloading, as a component of the severe RV dysfunction appeared to be related to acute respiratory distress syndrome (ARDS). Sodium bicarbonate was provided for severe acidosis. Propofol, fentanyl, and...
cisatracurium were used to improve ventilator synchrony in severe ARDS. Veno-arterial extracorporeal membrane oxygenation (ECMO) was considered, though deemed of limited utility given the imminent risk of mortality with multiorgan system failure.

Within 24 h of the above interventions, the patient experienced significant clinical improvement with down-trending inflammatory markers (Table 1; Figure 4), titration off norepinephrine, vasopressin, dobutamine, and sodium bicarbonate infusions, and cessation of neuromuscular blockade. Continuous cardiac monitoring did not reveal any significant dysrhythmia. Repeat TTE 48 h after ICU admission demonstrated significant myocardial recovery, showing an LVEF of 64%, mild RV dysfunction, Grade 2 diastolic dysfunction, and a small circumferential pericardial effusion (Figure 3; Supplementary material online, Videos 3 and 4). Eventually undergoing tracheostomy before subsequent discharge from the ICU and hospital, the patient is currently undergoing a prolonged ventilatory wean at a long-term acute care facility.

Table 1  Laboratory studies at baseline and 48 h after tocilizumab

| Laboratory test               | Baseline | After tocilizumab | Reference range                      |
|-------------------------------|----------|-------------------|--------------------------------------|
| Sodium                        | 138      | 141               | 135-148 mEq/L                        |
| Potassium                     | 5.7      | 3.9               | 3.5-5.0 mEq/L                        |
| Chloride                      | 100      | 102               | 98-112 mEq/L                         |
| Bicarbonate                   | 16       | 24                | 24-31 mEq/L                          |
| Blood urea nitrogen           | 16       | 48                | 8-23 mg/dL                           |
| Creatinine                    | 0.94     | 1.98              | 0.50-0.90 mg/dL                      |
| Anion gap                     | 22       | 15                | 7-15 mEq/L                           |
| Lactic acid                   | 4.4      | 1.5               | 0.5-2.2 mmol/L                       |
| White blood cell count        | 28.76    | 11.84             | 4.50-11.00 \times 10^3 \mu L         |
| Red blood cell count          | 4.87     | 3.13              | 4.20-5.50 \times 10^3 \mu L          |
| Haemoglobin                   | 14.1     | 8.9               | 12.0-16.0 g/dL                       |
| Haematocrit                   | 45.2     | 28.2              | 37.0-47.0%                           |
| Platelet count                | 300      | 124               | 150-400 \times 10^3 \mu L            |
| Prothrombin time              | 20.4     | 17.5              | 11.5-14.5 s                          |
| International normalized ratio| 1.7      | 1.4               | 0.8-1.1                               |
| Partial thromoplastin time    | 41.6     | 25                | 23.0-36.0 s                          |
| D-dimer                       | >20.00   | 5.5               | 0-0.40 µg/mL                          |
| Fibrinogen                    | 740      | 472               | 200-450 mg/dL                        |
| Ferritin                      | 35 461   | 11 062            | 13-150 ng/mL                         |
| C-reactive protein            | 36.82    | 12.65             | 0-0.50 mg/dL                         |
| Triglycerides                 | 122      | 270               | 0-150 mg/dL                          |
| Alkaline phosphatase          | 165      | 124               | 35-104 U/L                           |
| Aspartate aminotransferase    | 576      | 678               | 5.0-50 U/L                           |
| Alanine aminotransferase      | 1495     | 719               | 10.0-35 U/L                          |
| Total bilirubin               | 0.6      | 0.6               | 0-1.2 U/L                            |
| Lactate dehydrogenase         | 3735     | 1292              | 87-225 U/L                           |
| Interleukin-6                 | 846      | 106               | 0-5 pg/mL                            |
| Brain natriuretic peptide     | 401      | 166               | 0-100 pg/mL                          |
| Troponin-I (first)            | 1.058    | Not Applicable    | 0-0.040 ng/mL                        |
| Troponin-I (second)           | Not Applicable | 1.682    | 0-0.040 ng/mL                        |
| Troponin-I (third)            | Not Applicable | 1.162    | 0-0.040 ng/mL                        |
**Discussion**

We report the first case of a patient with cardiogenic shock associated with SARS-CoV-2-induced cytokine storm, most probably sepsis-induced cardiomyopathy or Takotsubo syndrome, who survived without ECMO or mechanical circulatory support (MCS) after treatment with tocilizumab and supportive vasoactive medications.6–9

Sepsis-induced cardiomyopathy and Takotsubo syndrome share similar pathophysiology with the up-regulation of IL-6. In vitro models of IL-6 demonstrated direct negative inotropic effects on papillary muscle function and down-regulation of sarcoplasmic reticulum Ca2+ ATPase (SERCA2) in cardiomyocytes, and increased IL-6 has been shown to reduce myocardial contractility in vivo.10,11 The systemic up-regulation of proinflammatory cytokines such as IL-6 in SARS-CoV-2-induced cytokine storm may lead to cardiac infiltration by leucocytes and macrophages, resulting in a ‘myocardial stunning’, manifested as a transient depression of global systolic function. The potential confounding of other medications and the most effective dose of tocilizumab are questions that remain in this case. However, the phase III randomized clinical trial COVACTA for the evaluation of the safety and efficacy of tocilizumab in patients with severe COVID-19 pneumonia aims to answer the latter question.12

Additionally, the patient met many of the Heart Failure Association diagnostic criteria for Takotsubo syndrome, with an identifiable physical stressful trigger in SARS-CoV-2, wall motion abnormalities extending beyond a single epicardial vascular distribution, new and reversible ECG abnormalities, and a relatively small elevation in TnT.13 Though the degree of acute biventricular heart failure and shock exceeded the level of BNP elevation in our patient, BNP levels do not necessarily correlate with cardiac haemodynamic indices in patients with Takotsubo syndrome and may be <400 pg/mL.14

---

**Figure 2** Electrocardiogram before and after new-onset acute decompensated heart failure. (A) Electrocardiogram before development of acute decompensated heart failure showing sinus rhythm with premature supraventricular complexes. (B) Electrocardiogram during cardiogenic shock showing sinus tachycardia with T-wave inversion in V1–V3 and a shift in the QRS axis compared with the earlier study.

**Figure 3** Transthoracic echocardiography two-dimensional images during acute biventricular heart failure and 2 days after treatment with tocilizumab, dobutamine, norepinephrine, vasopressin, and inhaled epoprostenol. (A) Transthoracic echocardiography apical four-chamber view: severe global right ventricular and left ventricular hypokinesis with paradoxical septal motion and left ventricular ejection fraction of 25%. (B) Transthoracic echocardiography parasternal long-axis view 2 days after tocilizumab administration: complete recovery of left ventricular systolic function with ejection fraction of 64%, grade 2 diastolic dysfunction, and small circumferential pericardial effusion. (C) Transthoracic echocardiography apical four-chamber view 2 days after tocilizumab administration: mild right ventricular systolic dysfunction, much improved from the prior study.
Though no evaluation of coronary anatomy is a limitation, acute coronary syndrome (ACS) was excluded on clinical grounds as the underlying aetiology of acute biventricular heart failure due to the rapid recovery of LVEF in the absence of revascularization. Likewise, viral lymphocytic myocarditis was deemed less plausible given the discrepancy in cardiac biomarker elevation to the extent of myocardial dysfunction and rapid myocardial recovery within 48 h. A case of acute lymphocytic myocarditis associated with SARS-CoV-2 mimicking reverse Takotsubo syndrome has been reported recently, with myocardial recovery achieved at 7 days, though notably SARS-CoV-2 genomic testing of biopsied cardiomyocytes was negative and the patient improved in cardiac function before receiving any therapy directed against SARS-CoV-2.\(^1\) Though CMR and EMB could aid diagnosis, our patient was too haemodynamically unstable to undergo either test during the time at which either study would be of the most benefit.

In conclusion, we report the first case of acute biventricular heart failure complicated by cardiogenic shock associated with SARS-CoV-2-induced cytokine storm that resolved with tocilizumab and supportive medications alone, and without the assistance of ECMO or MCS. Tocilizumab may be considered as a therapeutic option for patients with cardiogenic shock in the setting of SARS-CoV-2-induced cytokine storm, as IL-6 blockade may revive myocardium stunned from sepsis-induced cardiomyopathy or Takotsubo syndrome.

**Lead author biography**

Kalyan Raghavendra Chitturi is finishing residency training at Houston Methodist Hospital and will be joining the University of Missouri for cardiology fellowship. He completed medical school at the University of North Texas Health Science Center and undergraduate studies at the University of Michigan - Ann Arbor. His research interests include cardiovascular outcomes in cardio-oncology, heart failure, and structural heart disease.

**Supplementary material**

Supplementary material is available at European Heart Journal – Case Reports online

**Acknowledgements**

We thank all the nurses, physicians, and intensive care staff at Houston Methodist for their tireless efforts caring for critically ill patients during the global pandemic.
Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

References
1. 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.
2. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6R) antagonist tocilizumab may be the key to reduce the mortality. Int J Antimicrob Agents 2020;55:105954.
3. Tamariz L, Hare JM. Inflammatory cytokines in heart failure: roles in aetiology and utility as biomarkers. Eur Heart J 2010;31:768–770.
4. Poriskovski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowski EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Peske B, Riley JP, Rosano GMC, Rutten LM, Ruschitzka F, Rutten FH, van der Meer P, ESC Scientific Documentation Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–2200.
5. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med 2020;46:846–848.
6. Zeng J-H, Liu Y-X, Yuan J, Wang F-X, Wu W-B, Li J-X, Wang L-F, Gao H, Wang Y, Dong C-F, Li Y-J, Xue X-J, Feng C, Liu L. First case of COVID-19 complicated with fulminant myocarditis: a case report and insights. Infection 2020;doi: 10.1007/s15010-020-01424-5.
7. Fried JA, Ramasubbu K, Bhatt R, Toupkara VK, Clerkin KJ, Horn E, Rabbani L, Brodie D, Jain SS, Kirtane A, Masouni A, Takeda K, Kumaraiah D, Burkhoff D, Leon M, Schwartz A, Ureil N, Sayer G. The variety of cardiovascular presentations of COVID-19. Circulation 2020;doi: 10.1161/CIRCULATIONAHA.120.047164.
8. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin J, Masouni A, Jain SS, Burkhoff D, Kumaraiah D, Rabbani L, Schwartz A, Ureil N. Coronavirus disease 2019 (COVID-19) and cardiovascular disease. Circulation 2020;141:1648–1655.
9. Tavazzi G, Pellegrini C, Maurelli M, Bellato M, Scuitti F, Bottazzi A, Sepe PA, Resasco T, Camporotondo R, Bruno R, Baldanti F, Paolucci S, Pelenghi S, Iotti GA, Mapioli F, Arbustini E. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. Eur J Heart Fail 2020;22:911–915.
10. Finkel MS, Odds CV, Jacob TD, Watkins SC, Hattler BG, Simmons RL. Negative inotropic effects of cytokines on the heart mediated by nitric oxide. Science 1992;257:387–389.
11. Villegas S, Villarreal FJ, Dillmann WH. Leukemia inhibitory factor and interleukin-6 downregulate sarcoplasmic reticulum Ca2+ ATPase (SERCA2) in cardiac myocytes. Basic Res Cardiol 2000;95:47–54.
12. ClinicalTrials.gov. Bethesda (MD): National Library of Medicine (US). 2020 April 8 – Identifier NCT04320615, A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients with Severe COVID-19 Pneumonia (COVACTA); https://clinicaltrials.gov/ct2/show/NCT04320615.
13. Lyon AR, Bossone E, Schneider B, Schehrt U, Citro R, Underwood SR, Sheppard MN, Fightree GA, Parodi G, Akashi Y, Ruschitzka F, Filippatos G, Mbeazza A, Omerovic E. Current state of knowledge on Takotsubo syndrome: a Position Statement from the Taskforce on Takotsubo Syndrome of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2016;18:8–27.
14. Ahmed KA, Madhavan M, Prasad A. Brain natriuretic peptide in apical ballooning syndrome (Takotsubo/stress cardiomyopathy): comparison with acute myocardial infarction. Coron Artery Dis 2012;23:259–264.
15. Sala S, Peretto G, Gramaglia 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 Takotsubo syndrome in a patient with SARS-CoV-2 respiratory infection. Eur Heart J 2020;41:1861–1862.