

COVID-19-associated takotsubo cardiomyopathy

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SUMMARY

The novel COVID-19 has had an unprecedented and devastating spread internationally. COVID-19 infection can lead to a number of cardiovascular sequelae, including heart failure, which may portend worse clinical outcomes. Here, we report a rare case of a 57-year-old woman who developed acute left ventricular systolic dysfunction with apical ballooning consistent with takotsubo cardiomyopathy (TCM), and mixed cardiogenic and septic shock in the setting of COVID-19 disease. We briefly review the pathophysiology and diagnosis of TCM (also described as apical ballooning syndrome and stress-induced cardiomyopathy). Additionally, this case highlights the importance of a multidisciplinary approach to clinical decision-making and resource allocation in diagnosis and management of critical illness in the setting of the ongoing international COVID-19 pandemic.

BACKGROUND

Since December 2019, there has been an unprecedented, rapid spread of the novel COVID-19 internationally. As of 17 May 2020, there have been 4 525 497 confirmed cases and 307 395 deaths from COVID-19 globally with a crude case-fatality rate of 6.8%, markedly higher than that of influenza at <0.1%.^{1 2}

COVID-19 disease has a wide clinical spectrum, ranging from asymptomatic infection to a mild upper respiratory tract illness, respiratory failure, shock, and in severe cases, death.^{3 4} Reports describe various cardiovascular complications from COVID-19 infection, including acute myocardial infarction, myocarditis, cardiomyopathy, arrhythmia and venous thromboembolism.^{2 4} This is a case of classic takotsubo cardiomyopathy (TCM) in the setting of COVID-19 infection.

CASE PRESENTATION

A 57-year-old woman presented to Rush University Medical Center, Chicago, Illinois 5 days after developing fevers up to 39.7°C. She had a history of Crohn's disease, for which she was on chronic immunosuppression with ustekinumab, emphysema and morbid obesity with body mass index of 51 kg/m². Aside from fever, she reported chills, sore throat, rhinorrhea, productive cough, progressive dyspnoea on exertion and increased use of albuterol inhalers in the days leading to her admission. She denied any recent travel outside of Chicago, Illinois. However, she reported exposure to several grandchildren with recent influenza-like symptoms.

On presentation, patient was febrile and haemodynamically stable, with oxygen saturation of 93% on room air. On physical examination, she had normal cardiovascular examination and wheezes on pulmonary

examination, without jugular venous distension or lower extremity oedema.

INVESTIGATIONS

Given high clinical suspicion for COVID-19 disease, she was immediately placed in isolation and underwent testing with a nasopharyngeal PCR swab. Admission vital signs were as follows: blood pressure 118/70 mm Hg, heart rate 89 beats/min, respiratory rate 18 breaths/min and oxygen saturation 93% on room air. Initial chest radiograph showed mild bibasilar linear subsegmental atelectasis. She was closely monitored and treated with intravenous fluid hydration, antipyretics and empiric antibiotics for presumed community-acquired pneumonia (ceftriaxone 2 g intravenous daily). Her COVID-19 PCR test resulted positive on day 2 of admission.

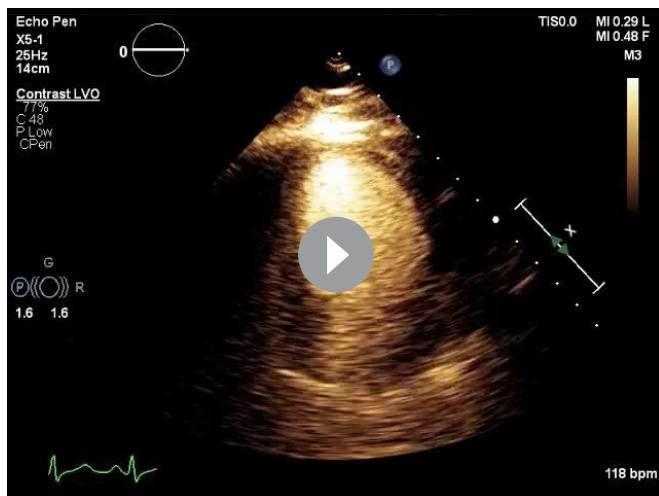
On the fourth day of hospitalisation, she had rapid deterioration of cardiorespiratory status, with oxygen saturation measured as low as 80% on 6 L/min O₂ flow delivered via nasal cannula, along with sinus tachycardia with heart rates averaging 130 beats/min, with fevers of maximum temperature of 40.1°C. Her repeat chest radiograph showed interval development of diffuse bilateral consolidative and ground-glass opacities. She was placed temporarily on non-invasive ventilation with a non-rebreather mask and transferred to the medical intensive care unit for escalation of care. Given worsening hypoxaemia, she underwent endotracheal intubation with lung protective ventilation strategy with high positive end expiratory pressures and low tidal volumes to treat the clinical picture of acute respiratory distress syndrome (ARDS). On the same day, the patient became hypotensive, requiring vasopressor support with norepinephrine (30 µg/min) and epinephrine (8 µg/min). Following this decompensation and COVID-19 diagnosis, antiviral medications (lopinavir 400 mg/ritonavir 100 mg by mouth every 12 hours) were started, along with initiation of a 5-day course of antimalarial agent (hydroxychloroquine two doses of 400 mg by mouth every 12 hours, followed by 200 mg by mouth every 12 hours). Antibiotics for possible bacterial superinfection were broadened simultaneously (intravenous vancomycin 25 mg/kg, intravenous cefepime 1 g every 12 hours, intravenous metronidazole 500 mg every 8 hours and intravenous azithromycin 500 mg daily).

Significant laboratory tests included: elevated serum troponin-I of 8.64 ng/mL (peaked to 10.09 ng/mL on day 5, normal: 0–0.09 ng/mL), creatine kinase within normal range initially (peaked to 5136 U/L on day 8, normal: 10–205 U/L) and elevated brain natriuretic peptide (BNP) to 112 pg/mL (peaked to 2060 pg/mL on day 7, normal: 0–100 pg/mL). D-dimer 4.07 mg/L (normal: 0–0.6 mg/L) and lactate dehydrogenase



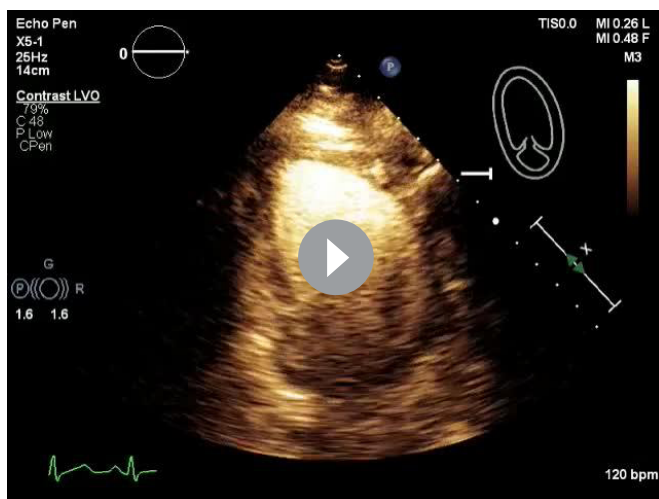
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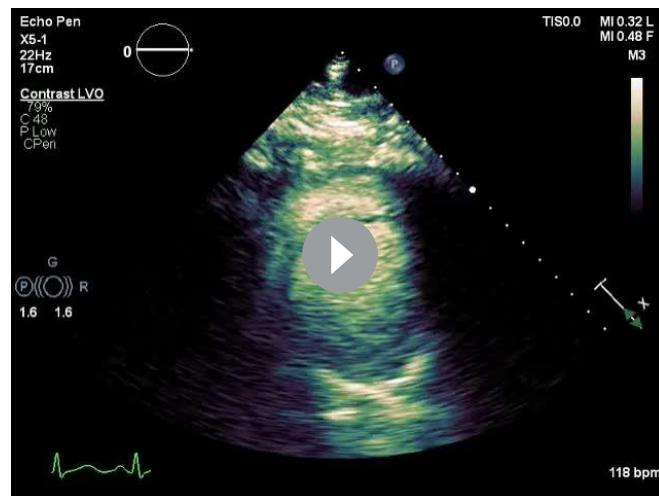


Video 1 Transthoracic echocardiogram contrast images in the apical four-chamber view showed severe hypokinesis in the mid-to-apical anterolateral and mid-to-apical inferoseptal segments of the left ventricle. Basal myocardial function was preserved.

350 U/L (normal: 110–240 U/L) were also abnormal. The patient developed oliguric acute kidney injury with creatinine elevation to 2.06 mg/dL (normal: 0.65–1.00 mg/dL) from a normal baseline. EKG showed sinus tachycardia without ST-wave or T-wave changes, prolonged QTc interval of 516 ms and low voltage QRS in the precordial leads. A transthoracic echocardiogram was performed on Hospital day 5, which revealed a severely depressed left ventricular ejection fraction of 25%–30%, with severe hypokinesis of the mid-to-apical segments and preserved basal myocardial function (videos 1–3). A coronary angiogram was considered but deferred at that time in light of the patient's progressive renal dysfunction and echocardiogram findings which were classically consistent with an alternate aetiology. A presumptive diagnosis of TCM was made based on the characteristic echocardiogram findings of apical ballooning, previously normal left ventricular systolic function, unremarkable past cardiac history and spontaneous improvement in serum troponin-I levels in the setting of a severe systemic illness.



Video 2 Transthoracic echocardiogram contrast images in the apical two-chamber view showed severe hypokinesis in the mid-to-apical anterior and mid-to-apical inferior walls, as well as normal function in the basal left ventricular segments.

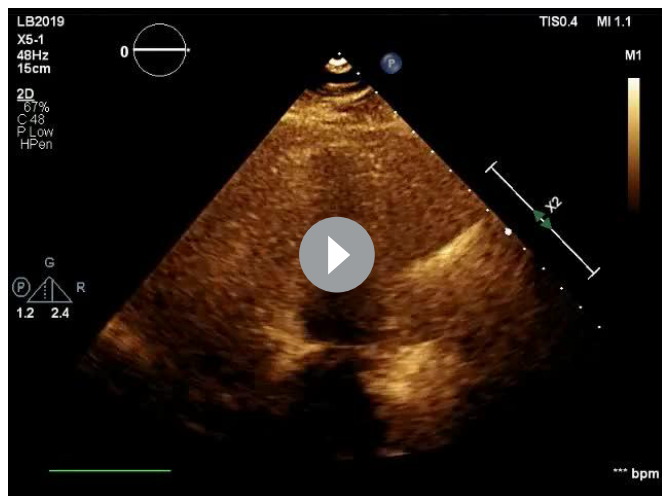


Video 3 Transthoracic echocardiogram contrast images in the parasternal short axis view showed hypokinesis in the mid segments of the left ventricle.

She remained hypotensive despite up titration of norepinephrine and epinephrine. A multidisciplinary meeting between the Advanced Heart Failure, Cardiovascular Surgery, and Pulmonary and Critical Care Medicine teams was held to evaluate her candidacy for advanced mechanical circulatory support (MCS). At present time, the role of MCS with venoarterial extracorporeal membrane oxygenation support (VA ECMO) in the management of cardiovascular collapse in COVID-19 remains unclear with experience scarce.⁵ In line with expert opinion, taking into consideration the health system's disease burden and capacity to offer a resource-intensive mode of support, a more stringent selection criteria was deemed to be the most appropriate approach, with priority given to those most likely to benefit from intervention as bridge to recovery. In this patient, her immunocompromised status, morbid obesity (body mass index ≥ 40) and severe multiorgan failure were criteria that made her less suitable for VA ECMO cannulation.⁶ Hence, aggressive medical management with meticulous supportive therapy was pursued.

Due to persistent hypotension and concern for combined cardiogenic and septic shock, dobutamine 5 $\mu\text{g}/\text{kg}/\text{min}$ was initiated for inotropic support, after which epinephrine was slowly weaned off. On hospital day 6, she was treated with a dose of interleukin 6 receptor antagonist (intravenous tocilizumab 800 mg). Over the following 2 weeks of her intensive care unit course, the patient's fever curve and renal function improved, with subsequent reduction in both vasopressor and inotropic requirements. She was weaned off norepinephrine and dobutamine on hospital day 11. However, she had recurrence of fevers on the third week of hospitalization, with a maximal temperature 40.7°C. Her blood cultures revealed fungaemia with *Candida albicans* for which she was treated with intravenous micafungin and oral fluconazole.

A follow-up chest radiograph on hospital day 18 demonstrated significant decrease in previously noted bilateral pulmonary opacities. Repeat transthoracic echocardiogram performed the same day for re-evaluation of cardiac function revealed complete resolution of left ventricular dysfunction with no appreciable regional wall abnormalities. The left ventricle was noted to be hyperdynamic with an estimated ejection fraction of 70%–75% (videos 4–6). A definite diagnosis of COVID-19-associated TCM was made. No further ischaemic evaluation was then pursued.



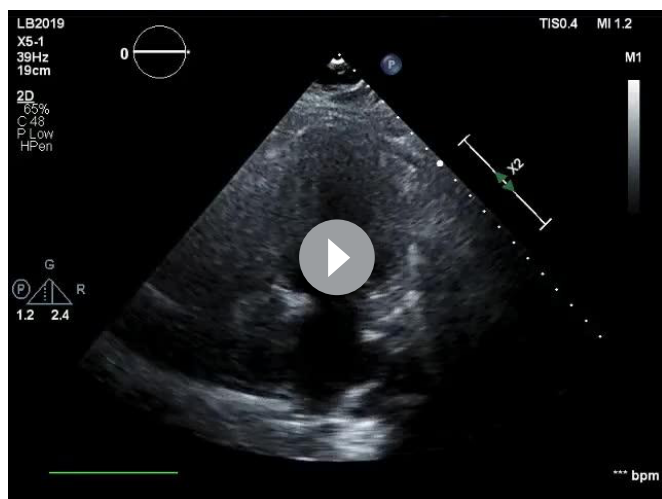
Video 4 Transthoracic echocardiogram images in the apical four-chamber view showed resolution of previously noted severe hypokinesis in the mid-to-apical anterolateral and mid-to-apical inferoseptal walls of the left ventricle.

DIFFERENTIAL DIAGNOSIS

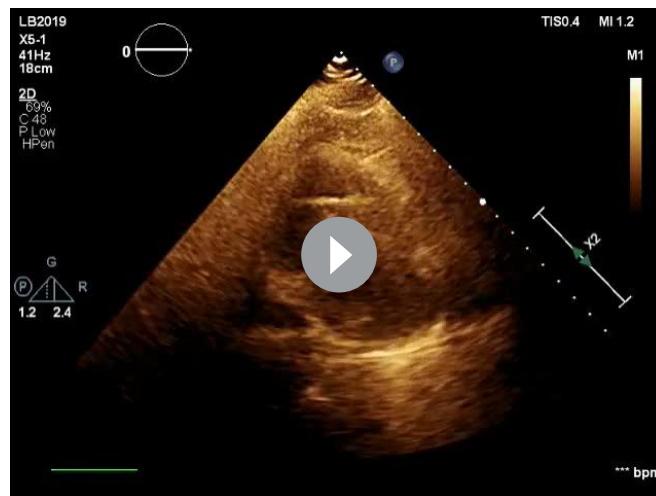
Alternative causes of elevated troponin and left ventricular dysfunction in this patient includes viral myocarditis and acute coronary syndrome (ACS). The patient had rapid recovery of her left ventricular systolic function within days, without steroid or anti-inflammatory therapy, and showed no evidence of electrical instability or arrhythmia, lowering suspicion for myocarditis. Additionally, though she had risk factors for coronary artery disease, her ejection fraction improved without revascularisation or intervention, suggesting her presentation was less likely to be due to coronary plaque rupture and ACS. This rapid recovery in left ventricular systolic function further supports the suspected diagnosis of TCM associated with COVID-19.

OUTCOME AND FOLLOW-UP

The patient required continued ventilatory support and underwent tracheostomy placement after 27 days of intubation. She remained



Video 5 Transthoracic echocardiogram images in the apical two-chamber view showed normalisation of previously noted severe hypokinesis of the mid-to-apical anterior and mid-to-apical inferior walls of the left ventricle.



Video 6 Transthoracic echocardiogram images in the parasternal short axis view showed recovery of previously seen hypokinesis in the mid segments of the left ventricle.

haemodynamically stable and was discharged to a long-term care facility for further care on hospital day 35.

DISCUSSION

COVID-19 disease, primarily affecting the lungs, appears to have a wide clinical spectrum, ranging from asymptomatic infection to a mild upper respiratory tract illness, severe viral pneumonia, respiratory failure, shock, and in severe cases, death.^{3,4} As our knowledge base continues to evolve on this new disease entity, we are starting to appreciate its complex multiorgan effects.

Several reports in the literature illustrate various cardiovascular complications of COVID-19 infection, including acute myocardial infarction, myocarditis, cardiomyopathy, arrhythmias and venous thromboembolism.²⁻⁴ The overlap of infectious symptoms of COVID-19 and classic symptoms of cardiac syndromes presents a diagnostic challenge in these patients; therefore, awareness of and vigilant surveillance for possible cardiovascular sequelae is critical. Patients can present with marked elevation in serum troponin-I level, abnormal electrocardiogram (EKG) and imaging findings (echocardiogram and cardiac MRI), and even evidence of inflammatory infiltration of myocardium consistent with myocarditis on autopsy.² Our case represents another cardiac manifestation of this infectious disease, with a classic presentation of TCM triggered by COVID-19. Rare cases of COVID-19-associated TCM have been described in the literature, often presenting with EKG changes including ST-elevation and or marked T-wave inversion, concerning for ACS, in contrast with our patient who had no evidence of ischaemic changes on EKG.⁷⁻¹⁹ Additionally, our case represents a severe case of COVID-19 disease with TCM in a severely immunocompromised patient in the background of Crohn's disease complicated by fungaemia, who had significant recovery after aggressive medical support.

First described in 1990, TCM, also referred to as broken heart syndrome or apical ballooning syndrome, is a transient, usually reversible, left ventricular systolic dysfunction that is classically described in women after exposure to an emotional or physical stressor.^{20,21} It derives its name from the Japanese term takotsubo, meaning 'octopus pot' to describe the ballooning of the apex, which is the most common presentation of this disease, seen in up to 81.7% of cases.²¹ The Mayo Clinic Criteria includes the following for TCM diagnosis: transient left ventricular hypokinesis, akinesis, or dyskinesis in the mid-segments with or without apical involvement,

commonly preceded by a stressful trigger, extension of wall motion abnormalities beyond a single epicardial vascular distribution, absence of obstructive coronary artery disease, new electrocardiographic abnormalities or modest cardiac troponin elevation, and absence of concomitant conditions.²² The International Takotsubo Diagnostic Criteria 2018 described a modification to the definition, to include other patterns of ventricular wall motion abnormalities, neurologic disorder as potential preceding event, significant elevation in BNP and a predominant demographic of postmenopausal women. In addition, this new guideline removed exclusion of significant coronary artery disease as criteria for diagnosis.²³ Based on these updated criteria, the diagnosis of TCM was made in our case.

Thirty years from the first description of TCM, the exact pathogenesis for this phenomenon remains unclear. Systemic viral illnesses such as influenza have been linked to stress cardiomyopathy in the existing literature.²⁴ Several proposed mechanisms in the setting of viral illnesses may be responsible, including sympathetic nervous system stimulation, hormonal pathways particularly oestrogen deficiency, and excess deposition of extracellular matrix.²⁰

In this patient who developed severe COVID-19 disease with multiorgan failure, a multitude of pathophysiologic mechanisms may have contributed. It is conceivable that acute illness, shock, and profound hypoxia with ARDS may have triggered surge of catecholamines leading to myocardial stunning. ACE2, the receptor for SARS-CoV-2 virus, known to be expressed in myocytes and vascular endothelium, could be an underlying mechanism for direct myocardial injury in COVID-19 disease. Patients with COVID-19 have been shown to have elevated levels of proinflammatory cytokines such as IL1B, IFN γ , IP10, MCP1, GCSE, MIP1A and TNF α , with higher concentrations associated with worse disease severity.²⁵ The cytokine storm brought about by overwhelming systemic COVID-19 disease could have been the physical and chemical stressor. These factors, in combination to our patient's baseline demographic characteristics, that of a postmenopausal female, may have ultimately led to the development of TCM.

Learning points

- ▶ Recognise takotsubo cardiomyopathy (TCM) and cardiogenic shock as a cardiovascular complication of COVID-19 disease.
- ▶ Discuss possible mechanisms for development of TCM in COVID-19 disease.
- ▶ Describe the management of combined cardiogenic and septic shock secondary to TCM and severe COVID-19 disease.
- ▶ Describe a multidisciplinary team approach to resource allocation of advanced mechanical circulatory support in the midst of the ongoing international COVID-19 pandemic.

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Contributors JMDG is this case report's first author, as she was in part of case report conception and design, patient data interpretation, initial article drafting and subsequent revisions, and direct patient clinical care. She has given final approval of this manuscript. GN was instrumental in manuscript writing drafting and revisions. She has given final approval of this manuscript. PN, AR, and KM are some of the attending physicians who supervised the writing of this case report. They were part of direct patient clinical care and were vital in case report design and article revisions. They have given final approval of this manuscript. TS is the main supervising attending physician of this case report. She was part of direct patient clinical care, and provided critical input in case report design and article revisions. She has given final approval of this manuscript.

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