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Case Reports

Takotsubo Syndrome Presenting as Cardiogenic Shock in Patients With COVID-19: A Case Series and Review of Current Literature

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ABSTRACT

Takotsubo's syndrome (TTS) is a form of stress cardiomyopathy with a relatively benign long-term course, but may lead to arrhythmias and cardiogenic shock in the acute setting. Despite a recent rise in suspected stress-induced cardiomyopathy, the relationship between the novel coronavirus disease 19 (COVID-19) and TTS is not fully understood. Early recognition of TTS in these patients is important to guide management and treatment. We present 2 cases of TTS arising in the setting of COVID-19 with rapid progression to biventricular heart failure and cardiogenic shock.

1. Introduction

Cardiovascular complications of the current coronavirus disease 2019 (COVID-19) pandemic are becoming increasingly recognized, with pathology ranging from acute coronary syndrome and vascular disease to myocarditis and cardiogenic shock [1,2]. Takotsubo syndrome (TTS), a non-ischemic cardiomyopathy thought to be due to excess catecholamines and sympathetic stimulation, has been well-recognized as a complication of severe sepsis and has been associated with increased rates of in-hospital mortality [3,4]. The association between the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and TTS, however, is not well understood. As rates of COVID-19 once again rise in the United States, we describe the presentation of two patients with SARS-CoV-2 infections who developed TTS, rapid biventricular heart failure, and cardiogenic shock, highlighting the need for early detection and treatment of this pathology in these patients.

2. Case 1

An 88-year-old man with metastatic prostate cancer treated with chemotherapy and advanced dementia presented to the emergency department (ED) with generalized weakness, fatigue, poor oral intake, and subjective fevers for several days. The patient was found to be SARS-CoV-2 positive by polymerase chain reaction (PCR) testing with elevated inflammatory markers (ferritin 538 ng/mL, C-reactive protein 115 mg/L, D-dimer 2.05 μg/mL). He was hypoxic requiring 2 L of nasal cannula, but hemodynamically stable. Within the first day of admission, the patient became tachycardic, and electrocardiogram (ECG) showed anteroseptal ST-segment elevations (Fig. 1A) with initial high-sensitivity cardiac troponin-T (hs-cTnT) value of 1604 ng/L. Despite his co-morbid conditions, his family emphasized his ability to care for himself prior to admission and given his acute decline, the decision was made to take him to the cardiac catheterization laboratory (CCL) for possible percutaneous coronary intervention, with the understanding that he would not be a candidate for advanced mechanical circulatory support. Coronary angiogram revealed mild non-obstructive coronary artery disease, and a left ventriculogram was performed which demonstrated preserved basal function with apical akinesis, consistent with TTS (Video 1). Pulmonary angiogram demonstrated no evidence of proximal filling defects concerning for large pulmonary embolism. A right heart catheterization revealed elevated biventricular elevated filling pressures with reduced cardiac output (CO) and cardiac index (CI), consistent with cardiogenic shock (Table 1).

It was thought that the patient's non-obstructive coronary disease was not the cause of the ST-segment elevations and there was no evidence of thrombotic disease. Peripheral vasodilators were given to decrease afterload, but no mechanical support was given due to co-morbidites and age. Shortly after the patient returned from the CCL, he was intubated for impending respiratory collapse and went into

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronarvirus 2; COVID-19, coronavirus disease 2019; ECG, electrocardiogram; ED, emergency department; CCL, cardiac catheterization laboratory; hs-cTnT, high-sensitivity cardiac troponin-T; LVOTO, left ventricular outflow tract obstruction; TTS, Takotsubo's syndrome.

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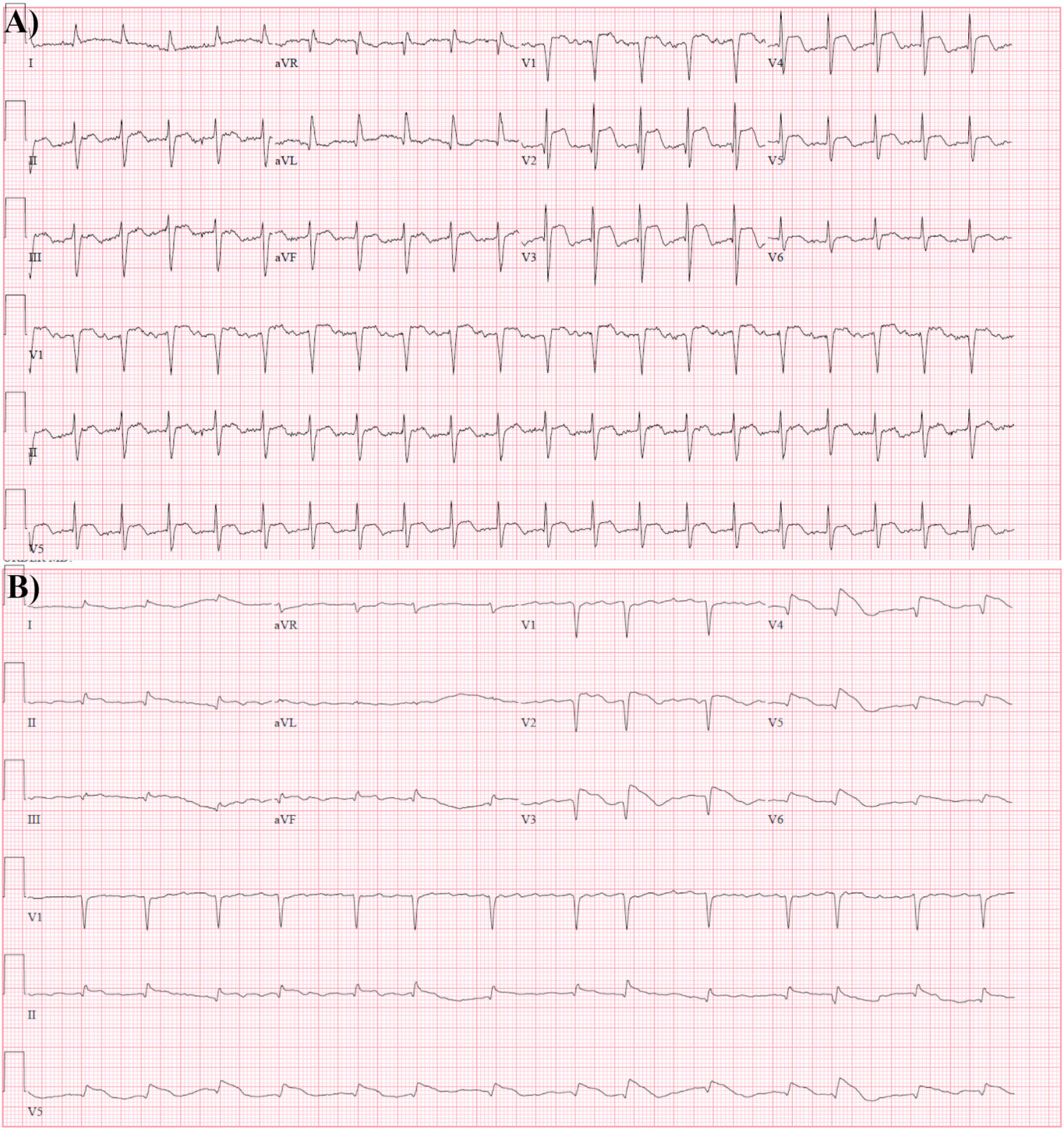

Fig. 1. (A) Electrocardiogram from patient 1 showing anteroseptal ST-segment elevations. (B) Electrocardiogram from patient 2 showing anteroseptal ST-segment elevations.

pulseless electrical activity arrest. Despite cardiac resuscitation, pulse was unable to be restored, and the patient was pronounced deceased within 24 h of his initial presentation.

3. Case 2

A 79-year-old woman with multiple sclerosis and known non-obstructive coronary artery disease was brought into the ED from her nursing home after being found altered and minimally responsive. On presentation, she was tachypneic and hypoxic on room air, requiring 5 L of supplemental oxygen via nasal cannula. She was febrile to 39.1C and was found to be SARS-CoV-2 positive by PCR, with elevated inflammatory markers (ferritin 1177 ng/mL, C-reactive protein 21 mg/L, ESR 37 mm/h, D-dimer 0.72 μg/mL).

The patient's respiratory status deteriorated within hours of presentation, requiring intubation. She underwent a computerized tomography scan of her chest with contrast which demonstrated no evidence of pulmonary embolism or pulmonary edema. On exam, the patient's extremities were now found to be cold and she became hypotensive, requiring initiation of norepinephrine and dopamine. ECG demonstrated new ST-segment elevations in the anterolateral leads (Fig. 1B) and hs-cTnT resulted at 2325 ng/L. The patient was taken for emergent

Table 1
Invasive hemodynamic measurements during right heart catheterization for each patient.

	Patient 1	Patient 2
Right atrium (mmHg)	12	10
Pulmonary artery, systolic (mmHg)	48	45
Pulmonary artery, diastolic (mmHg)	23	25
Pulmonary artery, mean (mmHg)	30	35
Pulmonary capillary wedge pressure (mmHg)	24	20
Pulmonary artery saturation (%)	50.3	37.7
Fick cardiac output (L/min)	3.2	1.9
Fick cardiac index (L/min/m^2)	1.7	1.2
Systemic vascular resistance (dynes*s/cm^5)	3190	2400
Pulmonary vascular resistance (Wood units)	1.9	5.2
Vasoactive agents	None	Norepinephrine[a] Dopamine[a]

[a] Medication was delivered via continuous infusion.

coronary angiography, which revealed non-obstructive coronary artery disease. A left ventriculogram demonstrated significantly reduced ejection fraction with preserved basal function and apical ballooning and akinesis, consistent with TTS (Video 2). Right heart catheterization showed elevated biventricular filling pressures with reduction in CO and CI (Table 1). A subsequent echocardiogram demonstrated an estimated left ventricular ejection fraction of 28.9% with apical hypokinesis, consistent with ventriculogram findings (Video 3).

The patient underwent placement of femoral intra-aortic balloon pump with improvement of her hemodynamics and mixed venous oxygenation. She was started on intravenous dexamethasone and remdesivir, although antiviral therapy was discontinued due to liver toxicity. She was weaned off vasoactive agents and mechanical support was removed on hospital day 3. She was successfully extubated on hospital day 10, and she was successfully discharged to her nursing home on guideline-directed medical therapy.

4. Discussion

Our series of two patients within the same week presenting with TTS complicated by cardiogenic shock in the setting of SARS-CoV-2 infection adds to previous isolated reports of TTS in COVID-19 patients and highlights the variable presentation and rapid hemodynamic collapse that can occur [4]. A previous study found an incidence of echocardiographic findings consistent with TTS in COVID-19 patients to be just over 4% [5]. Interestingly, although women are more commonly affected by TTS, the authors found that in this population, men, who are more likely to develop complications of COVID-19, made up all of the identifiable cases of TTS. We suggest that TTS may be under-recognized in patients with COVID-19 and should be considered in those presenting with arrhythmias, rapid hemodynamic decline, cardiac biomarker elevation, or ST-segment abnormalities.

The current pandemic has caused many CCL to change their policies for urgent catheterization. Our hospital follows the European Society for Cardiology's guidance statement, with urgent catheterization performed for STEMI and high-risk NSTEMI cases and all providers wearing full personal protective equipment [6]. Non-invasive evaluations may be beneficial to minimize exposure risk. However, diagnostic criteria for TTS vary based on societal guidelines, including regarding the presence of coronary disease. Non-invasive imaging criteria have not been validated for the diagnosis of TTS, and coronary angiogram with left ventriculogram remains the gold standard [3]. Although invasive testing increases SARS-CoV-2 exposure risk, it allows for exclusion of obstructive coronary disease (particularly given descriptive reports of thrombotic disease in these patients), and allows for assessment of hemodynamics to determine if mechanical circulatory support is required.

In patients with suspected TTS, rapid evaluation with echocardiography should still be performed. Although not diagnostic for TTS, echocardiography can provide information regarding the presence or absence of left ventricular outflow tract obstruction (LVOTO) that is estimated to occur in 10–25% of cases [8–10]. The use of inotropes in the presence of moderate to severe LVOTO is contraindicated; instead, these patients should be treated similarly to those with hypertrophic cardiomyopathy. Fluid administration is recommended in the absence of significant pulmonary congestion. Beta-blockade and the use of alpha-agonists have been shown to have benefit, while the use of inotropes has been shown to increase mortality [11].

The exact mechanisms behind TTS are not well understood, particularly in the case of COVID-19 infection. Multiple theories have been proposed for the development of TTS, including coronary microvascular dysfunction, catecholamine-induced myocardial stunning and

Table 2
Published case reports of Takotsubo cardiomyopathy in COVID-19.

Reference	Patients	Method of diagnosis	Notes
Roca et al. *Eur J Case Rep Intern Med.*	87yo female with hx of breast CA, no CV risk factors	Pattern on echocardiography, EF 48%	Elevated Tn-I, T wave inversions
Gustino et al. *J Am Coll Cardiol.*	5 patients, all male, age 39–65 yrs. compared with COVID+ pts. without suggestive echocardiogram	Echocardiography, EF 36% (35%–37%)	Higher rates of troponin, LV dysfunction, respiratory dysfunction, kidney injury, and death compared to non-TTS
Minhas et al. *JACC Case Rep.*	58yo female with hx of HTN, DM, and DLD	Echocardiography (EF 20%, mildly reduced RV function)	ST changes, elevated troponin, developed cardiogenic shock
Gomez et al. *BMJ Case Rep.*	57yo female with hx of Crohn's	Echocardiography (EF 25–30%)	Elevated troponin, developed cardiogenic shock and renal dysfunction
Taza et al. *BMJ Case Rep.*	52yo male with HTN and DM	Angiography with left ventriculogram demonstrating EF ~45%	Normal troponin but developed ST elevation in inferior leads
Dabbagh et al. *JACC Case Rep.*	67yo female with hx of NICM with recovery on medical therapy (15% to 40%)	Echocardiography	Elevated troponin, T wave abnormalities, no chest pain; new wall motion abnormalities
Meyer et al. *Eur Heart J.*	83yo female with hx of HTN	Angiography with left ventriculogram demonstrating apical ballooning	Elevated troponin, ST changes; improved EF with medical therapy
Nguyen et al. *Eur Heart J Cardiovasc Imaging*	71yo female with hx of HTN, HLD, and normotensive hydrocephalus	Angiography demonstrating coronary disease but left ventriculogram with wall motion abnormalities not explained by coronary disease	Elevated troponin, normal ECG
Solano-Lopez et al. *Eur Heart J.*	50yo male with hx of benign mediastinal tumor	Echocardiography followed by angiography and left ventriculogram	ST elevation, mild elevation in troponin, hypotension; atypical wall motion on echo with improvement by discharge
Pasqualetto et al. *Eur J Case Rep Intern Med.*	3 patients (2 male, 1 female), all age 80 and above, with HTN and DM	Echocardiography with reduction in EF and wall motion abnormalities	T wave changes, most severe decline in EF (30%) was in female patient and resulted in mortality

inflammation, and myocardial microinfarction [12]. COVID-19 has been associated with increased systemic inflammation leading to cytokine storm and may account for myocardial edema that has been noted in TTS patients [13,14]. This may also result in significant disruption of vascular endothelium, which can lead to microvascular dysfunction and microinfarction [15].

Cardiogenic shock is a known complication of TTS, occurring in approximately 10% of affected patients [16]. Rates of cardiogenic shock in patients with COVID-19 and TTS, however, are unknown. We have presented two sequential cases of patients with COVID-19 and TTS, both developing rapid cardiogenic shock requiring vasoactive medications. In both cases, right heart catheterization confirmed high filling pressures and cardiogenic shock, raising the possibility that cardiogenic shock may be present in a higher percentage of patients with TTS complicating COVID-19 infection. Other notable features of these cases are that neither patient had a known history of left ventricular dysfunction, which may predispose to increased mortality with TTS. Additionally, both patients had rapid hemodynamic collapse within 24 h of presentation with cardiac enzyme elevation and ECG changes without development of chest pain.

Our findings, particularly invasive hemodynamics, add to previously previous reports of TTS in the setting of COVID-19 (Table 2) [5,16–24]. A majority of previous reports have relied on non-invasive mechanisms for diagnosis as centers try to minimize patient exposure of known positive patients. This may, however, result in inaccurate estimations of TTS due to significant variation in TTS patterns and the fact that coronary disease can present with similar wall motion abnormalities. The effect this has on treatment and long-term outcomes is unknown. Our cases follow current gold-standard for diagnosis with angiography and left ventriculogram, although we recognize that clinical context and institutional guidelines need to be considered when identifying and treating these patients.

5. Conclusion

These cases highlight the rapid progression of life-threatening extrapulmonary complications of COVID-19. In the setting of arrhythmias, rapid hemodynamic decline, cardiac biomarker elevation, or ST-segment abnormalities, TTS should remain on the differential, as early diagnosis, recognition of high-risk features, hemodynamic assessment, and respiratory protection and/or hemodynamic support may affect clinical course.

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Declaration of Competing Interest

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