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Spectrum of Suspected Cardiomyopathy Due to COVID-19: A Case Series

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Abstract: The effects of COVID-19 on the cardiovascular system remains understudied given the early stage of the pandemic. Several case series and case reports have been published on COVID-19 related cardiomyopathies; however, there is often a lack of baseline echocardiographic data confirming a normal cardiac health prior to infection. Here we examine four patients with preserved left ventricular systolic function on prior echocardiogram who developed *de novo* cardiomyopathies which following COVID-19 infection. The study comprised of four individuals with an average age of 80.5 years, 75% of which were white males. 50% of cases were suspected to have Takotsubo CM vs. myocarditis while the remaining half were diagnosed as myocarditis. Left ventricular systolic function dropped from a normal range to an average of 30% during COVID-19 infection in these individuals. Moreover, half of the cases later died. In conclusion, the COVID-19 pandemic has demonstrated its ability to cause several serious cardiovascular complications with associated worsening of prognosis. Repeat TTE showed recovery of systolic

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function in 50% of the patients included. There does not appear to be any correlation between COVID-19 related treatments, age, or level of inflammatory markers in those who recovered systolic function versus those who remained depressed. Given the minimal literature on this topic, it is evident more information is needed to help advance treatment and understanding of COVID-19 induced cardiomyopathies; particularly if the vaccination fails to protect against novel strains of COVID-19 and the virus becomes endemic. (Curr Probl Cardiol 2021;46:100926.)

Introduction

The effects of COVID-19 on the cardiovascular system remains understudied given the early stage of the pandemic. Current research suggests COVID-19 can cause a broad spectrum of cardiac injuries and cardiomyopathies (CM) such as myocarditis, stress, or ischemic. Numerous mechanisms have been proposed which include direct myocardial injury from the cytokine storm, down regulation of angiotensin converting enzyme 2 (ACE2) receptors, and supply/demand mismatch.¹ Many are felt to be related to the severe inflammatory response; however, this link remains an area of intense research. Regardless of the cause, COVID-19 associated CM can severely worsen morbidity and mortality during active infection and have unclear long-term implications; therefore, more research is needed to direct therapy.

Several case series and case reports have been published on COVID-19 related cardiomyopathies; however, there is often a lack of baseline echocardiographic data confirming a normal cardiac health prior to infection. Here we examine 4 patients with preserved LVEF on prior echocardiogram who developed *de novo* cardiomyopathies following COVID-19 infection. Also, we demonstrate that some of these patients regained their systolic function following resolution of their acute illness suggesting a reversible cardiomyopathy in patients managed promptly.

Case 1

78-year-old Caucasian male presented with acute onset confusion and shortness of breath. Past medical history of hypertension, coronary artery disease, chronic kidney disease stage 3, and atrial flutter. Previous cardiac history was notable for prior negative nuclear stress test (2019) and prior

transthoracic echocardiogram (TTE) with left ventricular ejection fraction (LVEF) of 50% with no wall motion abnormalities (WMA) or significant valvular abnormalities (2019). The patient's vitals on arrival: 90s/50s, sinus tachycardia, mild tachypnea with RR of mid 20s, temp 102.2 F°, oxygen saturation of 85% on room air. Laboratory studies were notable for white blood cell count (WBC) of 8k/ μ L with 87% granulocytes and 5.1% lymphocytes, a metabolic panel demonstrating BUN 44 mg/dL, Cr 2.1 mg/dL (at baseline), ferritin 815 ng/mL, CRP 183 mg/L, CPK 3039 U/L, lactic acid 1.9 mmol/L, mildly elevated LFT's, troponin 0.067 ng/mL. Supine 1 view chest x-ray revealed bilateral pulmonary infiltrates. Shortly after presentation patient decompensated and was intubated. The patient was started on ceftriaxone, azithromycin, steroids, hydroxychloroquine, and vasopressors. Transthoracic echocardiography (TTE) revealed newly depressed LVEF of 25% with basal-sparing and severe apical akinesis. Electrocardiogram (EKG) showed new nonspecific ST/T wave changes. Troponin peaked at 2.17 ng/mL. Cardiology was consulted with concerns for Takotsubo CM vs myocarditis. Inotropes were held given possibility of Takotsubo CM and hydroxychloroquine was discontinued on day 2. Patient developed progressive multiorgan failure, requiring dialysis, and unfortunately expired on day 4 of hospitalization.

Case 2

95-year-old Caucasian male presented with fever and cough. Past medical history of coronary artery disease, hypertension, and cerebrovascular accident (2016). Cardiac history notable for NSTEMI with drug-eluting stent to left circumflex artery and ramus artery (2016) and LVEF 55% with grade I diastolic dysfunction, moderate tricuspid regurgitation, and no WMAs (2016). The patient's vitals on arrival: normotensive, HR 140s in atrial fibrillation, tachypneic, temp 100 F°, oxygen saturation of 90% on RA. Initial laboratory studies were notable for WBC 18k/ μ L with 93% granulocytes and 1.4% lymphocytes, a metabolic panel demonstrating BUN 19 mg/dL, Cr 1.2 mg/dL (at baseline), CRP 178 mg/L, lactic acid 1.2 mmol/L, troponin 0.329 ng/mL. CXR revealed bilateral multifocal infiltrates. Supplemental oxygen by nasal canula was initiated alongside broad-spectrum antibiotics (vancomycin, cefepime). Glucocorticoids and hydroxychloroquine were held due to unclear benefit at time of presentation. A TTE was performed which showed a LVEF of 35% with no focal WMAs or valvular abnormalities. Initial EKG showed atrial fibrillation with RVR and no acute focal ischemic changes. Peak troponin 0.796 ng/mL. Oxygenation requirements eventually improved to 3L NC and

patient was discharged to a skilled nursing facility on day 16 of hospitalization. He was continued on a beta blocker and ACE inhibitor, both prescribed prior to admission. Approximately 3 months later, patient was readmitted for hypothyroid symptoms with AMS and UTI. Patient continued to decompensate during this admission. After goals of care discussions with palliative medicine, he was transitioned to hospice care and expired a short time thereafter. Repeat TTE 4 months after COVID-19 infection showed persistently depressed LVEF of 35% with no wall motion abnormalities.

Case 3

76-year-old Caucasian male presented with worsening cough, SOB, fever, and lightheadedness. Past medical history of diabetes, hypertension, and hyperlipidemia. Cardiac history notable for negative SPECT (2014) and LVEF 55% with mild diastolic dysfunction, no WMAs, and no significant valvular abnormalities (2014). Vitals on arrival: normotensive, sinus tachycardia, RR of 14, afebrile, oxygen saturation 90% on RA. Initial labs: WBC 7k/ μ L with 80% granulocytes and 10% lymphocytes, BUN 17 mg/dL, Cr 1 mg/dL (at baseline), ferritin 1656 ng/mL, CRP 46 mg/L, CPK 171 U/L, lactic acid 1.5 mmol/L, mildly elevated LFT's, troponin 0.079 ng/mL. CXR showed bilateral multifocal infiltrates. Patient was initially started on empiric community acquired pneumonia treatment with azithromycin. Hydroxychloroquine was held for concern of QT prolongation. Shortly after admission he became hypotensive and was moved to the ICU for vasopressor requirements. Subsequently, started on broad spectrum antibiotics and steroids. Repeat EKGs showed diffuse t-wave inversions. Peak troponin 3.170 ng/mL. Cardiology was consulted due to initial concern of NSTEMI as cause of hypotension. Stat TTE showed LVEF of 30%, severely depressed LV systolic function, and global hypokinesis with akinesis of the apex and basal sparing. Given no chest pain, diffuse EKG pattern and TTE findings, there was a high likelihood for secondary myocarditis or Takotsubo CM. On hospital day 7, was weaned off oxygen and discharged home. Upon discharge, he was continued on a beta blocker and ACE inhibitor, both prescribed prior to admission. Repeat TTE 4 months after COVID-19 infection showed LVEF 55%-60% with no WMAs.

Case 4

73-year-old African American female presented with a one-week history of worsening dyspnea, nonproductive cough, chest tightness, chills

and diaphoresis. Past medical history of chronic kidney disease stage 4, diabetes, coronary artery disease, and diastolic heart failure. Cardiac history notable for negative stress echo (2017) and LVEF 55% with diastolic dysfunction, no WMAs, and no significant valvular abnormalities (2016). Vitals on arrival: normotensive, normal sinus rhythm, mild tachypnea, afebrile, oxygen saturation 95% on RA. Initial labs: WBC 8k/ μ L with 76% granulocytes and 16% lymphocytes, BUN 67 mg/dL, Cr 5.1 mg/dL (baseline Cr 2.5), ferritin 1252 ng/mL, CRP 8 mg/L, CPK 73 U/L, lactic acid 1 mmol/L, minimally elevated LFT's, troponin 0.07 ng/ml. CXR revealed multifocal pneumonia. She was started on empiric ceftriaxone and azithromycin. Steroids and hydroxychloroquine were not given. TTE showed LVEF 40% with global hypokinesis. EKG showed nonspecific ST/T wave abnormalities. Peak troponin 0.71 ng/mL. Throughout 4-day hospital course, patient showed clinical improvement and was weaned off supplemental oxygen. She was started on carvedilol but not on ACE-I/ARB therapy due to AKI on chronic kidney disease stage 4. Repeat TTE 1 month after COVID-19 infection showed LVEF of 55% with no wall motion abnormalities.

Discussion

Since the discovery of severe acute respiratory syndrome-coronavirus 2 (COVID-19), there has been a tremendous amount of research done on the implications of viral infection. Early in the global pandemic it became clear that COVID-19 would have huge cardiovascular consequences owing to the fact that the entry protein, ACE2, is heavily expressed in heart, vascular, and pulmonary tissue.¹ Acute myocardial injury, defined as an elevation in cardiac troponins, was common in hospitalized patients with COVID-19. In one review, between 8%-62% of hospitalized patients demonstrated elevated troponins with a wide range.^{3,4} It was found to be strongly associated with worse clinical outcomes initially from Wuhan and confirmed in other studies.^{1,5} Since this discovery, COVID-19 has been associated with numerous cardiovascular complications ranging from acute myocardial injury, arterial thrombosis, myocarditis, tachyarrhythmias, and acute cardiomyopathies.^{1,2} The diverse cardiovascular complications of COVID-19 are well highlighted in the above 4 cases.

Myocarditis was included in the differential diagnosis of all our cases; however, given the wall motion abnormalities seen on echo in Cases 1 and 3, Takotsubo CM was suspected. Takotsubo

cardiomyopathy (TTS) has been previously documented as associated with COVID-19 infection. Among COVID-19 patients receiving TTE, echocardiogram findings suggestive of stress cardiomyopathy was noted in 1.5%-5.6% of patients.^{6,7} A recent systematic review compiling 27 reported cases associated with COVID-19 was recently published which delineated a number of imaging characteristics including a proposed pathophysiologic mechanism for cytokine storm induced TTS.^{8,9} Additionally, patients with COVID-19 induced TTS were found to have higher mortality than patients with matched cardiovascular risk factors.⁸ In this case series, one of the two patients with suspected TTS expired; however, Case 3 had eventual recovery of systolic function. Of note, both cases of suspected TTS had significant elevation of troponin levels compared to the other patients, which may indicate a higher level of inflammation and myocardial damage, leading to a more severe cardiomyopathy such as TTS.

COVID-19 induced myocarditis is thought to occur via non-ischemic pathophysiology. Prior studies with endomyocardial biopsies have yielded classic T cell mediated inflammatory infiltrate and further characteristic MRI findings.¹⁰ Patients include in prior reports had drastically elevated biomarkers, global wall motion abnormalities, and require inotropic support for cardiogenic shock which frequently developed.¹⁰ Due to this similarity in presentation to stress cardiomyopathy, diagnosis must be made meticulously as inotropic support in TTS would worsen prognosis. In this case series, patients 2 and 4 appeared to have findings more consistent with myocarditis. Both patients had no focal ischemic changes on EKG, minimally elevated troponins, no angina, and a newly depressed LVEF. Unfortunately, given the COVID-19 positive status and early timing of the pandemic, our facility was limiting MRI use for COVID-19 patients; therefore, no definitive diagnosis of myocarditis could be established. Of the myocarditis patients, only Case 4 had recovery of systolic function; Case 2 did not have recovery of LVEF which may be secondary to patients age, deconditioning, and comorbid medical conditions. [Table 1.](#)

All patients in this case series were evaluated by cardiology and thought to not have acute coronary syndrome given the above-mentioned findings of non-localizing EKG and echo findings in absence of anginal type chest pains. Furthermore, 75% of the patients had follow up TTEs and EKGs with no noted wall motion abnormalities in coronary distribution or pathologic q-waves, respectively.

Table 1. Cardiomyopathy progression and treatment. Patient characteristics and summary of outcomes for presented patients with COVID-19 associated cardiomyopathy

Case	Age	PMH	Prior LVEF	Prior valvopathies	LVEF during COVID-19	WMAs during COVID-19	New Valvopathies during COVID-19	RHF during COVID-19	Peak Troponin during COVID-19	COVID-19 treatment	LVEF after discharge	Suspected etiology of CM	Outcome
1	78	HTN, CAD, CKD3, A. flutter	50%	Mild TR	25%	Severe apical akinesis with basal sparing	Moderate TR	No	2.17	Steroids, hydroxy-chloroquine	n/a	Takutsubo vs. Myocarditis	Died during COVID-19 admit
2	95	CAD, HTN, CVA	55%	Mild to moderate TR, mild MR, mild AR	35%	None	Mod to severe TR, mod MR, mild to mod. AR, mod. to severe AS, mild PR	No	0.796	None	35%	Myocarditis	No LVEF recovery, died after subsequent admit for unrelated cardiac issues
3	76	DM, HTN, HLD	55%	Mild MR, mild TR	30%	Global hypokinesis, apical akinesis, basal sparing	Valves not well visualized	Mildly reduced RVF	3.170	Steroids	55% -60%	Takutsubo vs. Myocarditis	Recovery of LVEF, alive
4	73	CKD4, DM, CAD, and HFpEF	55%	None	30%	Global hypokinesis	Mild to moderate TR	No	0.71	None	55%	Myocarditis	Recovery of LVEF, alive

A. Flutter, Atrial flutter; AR, aortic regurgitation; AS, atrial stenosis; CAD, coronary artery disease; CKD3/4, chronic kidney disease stage 3/stage4; CVA, cerebrovascular accident; DM, diabetes mellitus; HFpEF, heart failure preserved ejection fraction; HLD, hyperlipidemia; HTN, hypertension; MR, mitral regurgitation; RVF, right ventricular failure; TR, tricuspid regurgitation.

Conclusion

In conclusion, the COVID-19 pandemic has demonstrated its ability to cause several serious cardiovascular complications with associated worsening of prognosis. Here we presented four patients with suspected myocarditis or Takotsubo CM and varying outcomes. Repeat TTE showed recovery of systolic function in 50% of the patients included. Of these, both were restarted on goal directed medical therapy with exception of Case 4 where ACEi/ARB was held due to acute on ESRD. There does not appear to be any correlation between COVID-19 related treatments, age or level of inflammatory markers in those who recovered systolic function versus those who remained depressed. This may be partly due to concurrent comorbidities. Given the minimal literature on this topic, it is evident more information is needed to help advance treatment and understanding of COVID-19 induced cardiomyopathies; particularly if the vaccination fails to protect against novel strains of COVID-19 and the virus becomes endemic.

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