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PII: S2666-0849(20)30331-4

DOI: https://doi.org/10.1016/j.jaccas.2020.04.001

Reference: JACCAS 424

To appear in: *JACC Case Reports*

Received Date: 27 March 2020

Revised Date: 2 April 2020

Accepted Date: 6 April 2020

Please cite this article as: Chau VQ, Oliveros E, Mahmood K, Singhvi A, Lala A, Moss N, Gidwani U, Mancini DM, Pinney SP, Parikh A, The Imperfect Cytokine Storm: Severe COVID-19 with ARDS in Patient on Durable LVAD Support, *JACC Case Reports* (2020), doi: https://doi.org/10.1016/j.jaccas.2020.04.001.

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Running Title: Severe COVID-19 in Patient on Durable LVAD

Keywords: COVID-19; LVAD; ARDS; cytokine storm

Disclosure Statement: Dr. Pinney serves as a consultant for Abbott Laboratories, CareDx, Medtronic, and Procyrion. All other authors have no conflicts of interest to disclose.

Abbreviations:
ARDS = acute respiratory distress syndrome
COVID-19 = coronavirus disease 2019
LVAD = left ventricular assist device
MODS = multiorgan dysfunction syndrome
PEA = pulseless electrical activity
PI event = pulsatility index event
RV = right ventricle
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Abstract

As health systems worldwide grapple with the COVID-19 pandemic, patients on durable LVAD support represent a unique population at risk for the disease. We outline such a patient who developed COVID-19 complicated by “cytokine storm” with severe ARDS and myocardial injury; and describe the challenges that arose during management.

History of Presentation

The patient is a 70-year-old male with a destination therapy HeartMate 3 left ventricular assist device (LVAD) implanted in 2016 who developed fever, flank pain and hematuria three days after attending a party. He was evaluated for nephrolithiasis at a local emergency department (ED) with CT abdomen and pelvis which incidentally found possible atypical or viral pneumonia. He was tested for coronavirus disease 2019 (COVID-19), but he left against medical advice. In the ensuing days, he continued to have fevers, new onset myalgias, diarrhea, and dyspnea. He returned to our ED and was in acute hypoxic respiratory failure, requiring supplemental oxygen to maintain peripheral oxygen saturation ≥94%.

Past Medical History

His medical history includes ischemic cardiomyopathy, stage 3 chronic kidney disease, and obesity. His post-LVAD complications include gastrointestinal bleeding, ventricular tachycardia, and right ventricular (RV) dysfunction, but no infectious complications. He does not have diabetes or tobacco use. His blood group is A positive.

Differential Diagnosis

Pretest probability for COVID-19 was moderate to high due to fever, dyspnea, and hypoxia as well as prior imaging showing peripheral ground-glass opacities.

Investigations

Reverse transcription polymerase chain reaction (RT-PCR) for severe acute respiratory syndrome coronavirus 2 (SAR-CoV-2) was positive at the initial ED visit and at our institution. Serial laboratory and imaging tests are detailed in Table 1. Several markers of disease severity were abnormal including absolute lymphocyte count, C-reactive protein and cardiac enzymes. Chest X-ray showed bilateral infiltrates concerning for atypical pneumonia (Figure 1).

Management

The patient was quarantined in a negative-pressure intensive care room. Figure 1 details his clinical course. Based on our Mount Sinai protocol (Figure 2), the patient was initiated on hydroxychloroquine for COVID-19 pneumonia while monitoring the QTc. He experienced severe acute respiratory distress syndrome (ARDS) necessitating endotracheal intubation and ventilator support with low tidal volume ARDSNet protocol. Despite aggressive supportive care, "cytokine storm" ensued with MODS as evidenced by 1) elevated inflammatory markers; 2) severe ARDS; 3) myocardial injury; and 4) vasodilatory shock requiring vasopressors. Two successive doses of intravenous tocilizumab (interleukin-6 [IL-6] receptor antagonist) at 8 mg/kg (max dose of 800mg) were administered. Though clinical improvement was observed after initial tocilizumab therapy, he developed worsening shock, refractory hypoxemia, and suffered pulseless electrical activity (PEA) arrest with successful return of spontaneous circulation.

Discussion

COVID-19 is a pandemic caused by the novel coronavirus SARS-CoV-2 and has taken a stronghold in New York State [1]. Patients with heart failure on LVAD support is a unique population at risk for COVID-19. We present such a patient who developed COVID-19 complicated by "cytokine storm" with severe ARDS and myocardial injury and illustrate clinical considerations that arose during his clinical course.

Inflammation and COVID-19 in LVAD support.

The host response to COVID-19 is often localized in the lung parenchyma, but a surge in pro-inflammatory cytokines can occur [2,3]. Known as a "cytokine storm," this phenomenon is described in graft-versus-host disease and viral illnesses including influenza and COVID-19 [2]. The complication is MODS including ARDS and cardiac manifestation. Biomarkers of COVID-

19 related cytokine storm include lymphopenia, C-reactive protein, lactate dehydrogenase (LDH), ferritin, D-dimer, and troponin [2-4]. Siddiqi and Mehra proposed a schema to assess severity of "systemic hyperinflammation" in COVID-19 to guide therapies [4]. Serial evaluation of inflammatory markers should be done to risk stratify the critically ill from patients with milder disease.

Inflammation and myocardial injury from COVID-19 must be differentiated from baseline inflammation often encountered during LVAD support [5]. In our LVAD patient, several biomarkers including LDH, absolute lymphocyte count, brain natriuretic peptide (BNP) and troponin have previously been obtained. In lieu of absolute values, the relative change in these biomarkers may be more pertinent in grading COVID-19 severity in patients on LVAD support. Our patient had increased inflammatory and cardiac biomarker profiles from baseline that worsened with disease progression. This inflammatory biomarker profile improved after tocilizumab. Changes in the pattern of these laboratory markers may be reliable tool to follow LVAD patients with COVID-19.

Cardiac Manifestations. Experience in China has shown that COVID-19 could adversely affect the cardiovascular system [3]. Our patient had evidence of myocardial injury as part of this COVID-19 presentation. The myocardial effect is likely a multifactorial process due to "bystander effect" from MODS, viral myocarditis, and activation of adverse remodeling mechanisms [3,4]. Furthermore, PEA arrest in our patient may be a sequela of such cardiac damage, and as such, LVAD support may have been instrumental in his resuscitation. In this context, management of patients on LVAD support with COVID-19 is difficult as there is a complex interplay between volume status and biventricular dynamics. We should closely

monitor for 1) RV failure and need for inotropic support; 2) LVAD speed drops or suction events, low flow, or pulsatility index (PI) events due to vasoplegia associated with infection.

Management Considerations.

To limit healthcare worker (HCW) exposure to COVID-19, nonessential testing such as echocardiograms, X-rays, CT and pulmonary artery catheters were deferred. Physical examination of jugular venous pressure, pulmonary crackles, and hepatojugular reflux are essential to making clinical decisions. Also, LVAD monitor displays of flow parameters maybe useful as a surrogate for cardiac output if the display flow correlates with prior invasive hemodynamic data.

Though there is no definitive therapy for COVID-19, there are multiple ongoing randomized trials evaluating different treatments [3]. The anti-malarial medication, hydroxychloroquine which was chosen as initial treatment for our patient, was shown to reduce *in vitro* SAR-CoV-2 cell entry, and a retrospective study suggested its clinical benefit in COVID-19 [3,4]. A major side effect is QTc prolongation, so our protocol provides monitoring guidance of this complication. Immunomodulatory biologics such as tocilizumab are reserved for *severe* COVID-19 defined by the presence of both worsening respiratory failure and cytokine storm as evidenced by increasing inflammatory markers. Still, caution is warranted as major adverse effects of tocilizumab include infection, infusion reactions, dyslipidemia, neutropenia, and potential malignancy [6]. Patients on LVAD support are particularly vulnerable to infectious complications due to the inherent presence of hardware and driveline exposure as well as the fact that prolonged support has been associated with immune dysregulation [5].

Finally, prone ventilation is beneficial in severe ARDS. The maneuver has been effective in improving lung mechanics and gas exchanges, and in some cases, it may prevent the need to

escalate to venous-venous extracorporeal membrane oxygenation [7,8]. Though there are no published outcomes, early experience in Wuhan, China indicates prone position was widely used in COVID-19 related severe ARDS with possible benefits [8]. Nonetheless, it may be prohibitive in heart failure patients on LVAD support. Prone positioning could result in complications such as compression of outflow graft and driveline, impaired venous return from increased thoracic pressure, hardware malpositioning, and worsening RV hemodynamics [9,10]. There may be additional anxiety for staff caring for COVID-19 patients, not otherwise familiar with LVAD management. Due to these considerations, prone ventilation was not performed in our patient. Its potential for benefit in LVAD supported patients with ARDS warrants further study.

Follow-Up

While his inflammatory profile improved after tocilizumab, he remained in critical condition on maximal ventilatory support and on vasopressors for shock. Given his multiple complications, early palliative care discussion was initiated. His MODS continued to worsen, and methylene blue was administered without improvement in hemodynamics. The patient ultimately expired on hospital day 8.

Conclusions

This case highlights a systematic approach and various considerations for a patient with an LVAD who developed life-threatening manifestations of COVID-19.

Learning Objectives

1. To describe high risk clinical features in a patient on durable LVAD support who developed COVID-19
2. To illustrate potential complications and clinical dilemmas in managing COVID-19 in a patient supported with a durable LVAD

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Figure Legends

Figure 1. Clinical course of severe COVID-19 in our patient on LVAD support.

Figure 2. Clinical guidance and considerations at Mount Sinai for managing COVID-19 in patients with LVAD support.

	Last Visit*	HoD 0	HoD 3**	HoD 6***

Table 1. Vitals and laboratory values of our patient with LVAD while receiving inpatient treatment for COVID-related cytokine storm with severe ARDS and multi-organ dysfunction

	Reference Values	Absolute Value	Absolute Value	Relative Change#	Absolute Value	Relative Change#	Absolute Value	Relative Change#
Max Temperature (°C)	36-37.9	36.6	38.5	5%	37.5	2%	37.8	3%
MAP (mmHg)	70-85	90	75	-17%	74	-18%	74	-18%
Pulse (bpm)	60-100	80	80	0%	80		80	0%
CVP (mmHg)	5-10	10			14	40%	10	0%
LVAD Speed (rpm)		5600	5600		5600		5600	
LVAD flow (lpm)		4.8	4.6	-4%	4.5	-6%	3.0	-38%
O2 Saturation (%)	92-100	98	90		98		100	
PaO2 (mmHg)	80-105				68		143	
FiO2 (%)		21	21		80		80	
PaO2 to FiO2 ratio	>300				85		178	
White blood cell (x10^3)	4.5-11	5.1	**3.0**	**-41%**	**6.1**	**20%**	**4.9**	**-4%**
Absolute Neutrophil (x10^3)	1.9-8.0	3.7	**2.0**	**-46%**	**4.9**	**32%**	**3.7**	**0%**
Absolute Lymphocyte (x10^3)	1.0-4.5	1.4	**0.7**	**-50%**	**0.8**	**-43%**	**0.7**	**-50%**
eGFR (mL/min/1.73m3)	>90	51	44	-14%	58	14%	55	8.0%
Urobilinogen	Negative	Negative	Negative					
AST (U/L)	1-35	19	69	263%	86	353%	121	537%
ALT (U/L)	1-45	8	11	38%	15	88%	24	200%
Total bilirubin (mg/dL)	0.1-1.2	1.0	1.0	0%	1.8	80%	1.6	60%
Direct bilirubin (mg/dL)	0.0-0.8		0.5		1.2		1.0	
Interleukin-1	<5		<5					
Interleukin-6	0.0-15.5		135		260		>3000	
C-reactive protein (mg/L)	0-5.0		75		158		63	
LDH (U/L)	100-220	247	**485**	**96%**	**802**	**225%**	**647**	**162%**
D-dimer (ug/mL)	0.00-0.50		1.32		1.1			
Ferritin (ng/mL)	30-400	23	376	1534%			719	3026%
Procalcitonin	<0.49		0.43		0.61		0.33	
Troponin (ng/mL)	0.00-0.03	0.02	0.1	400%	0.09	350%	0.33	1550%
CK-MB (ng/mL)	0.6-6.3				2.6		1.8	
Creatine Kinase (U/L)	30-200		1183		863		188	
BNP (pg/mL)	0-100	281	580	106%	721	157%	404	44%
Pro-BNP (pg/mL)	300-899		6075		4709		9820	
Lactate (mmol/L)	0.5-1.99		1.8		1.5		2.0	

Abbreviations: HoD = hospital day. MAP = mean arterial pressure (obtained from doppler or arterial line). CVP = central venous pressure (obtained from right heart catherization at baseline, and from central venous line in hospital). PaO2 = arterial partial pressure of oxygen. FiO2 = fraction of inspired oxygen. eGFR = estimated glomerular filtration rate. LDH = lactate dehydrogenase. Bold in-hospital values are those with consistent baseline values

*Last vist values were the latest values obtained within the last 6 months. Baseline LDH, WBC, platelet, absolute PMN, and absolute lymphocyte were recorded as an average of last three values within the one year

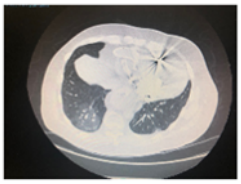
**Patient was placed on ventilator support on the night of HoD 2, and was given tocilizumab on the evening of HoD 3

***Patient suffered pulseless electrical activity arrest status post return of spontaneous circulation

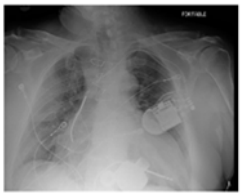
#Relative change is percentage increase or decrease from baseline value

Figure 1

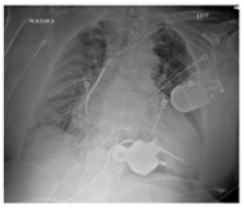
Case Timeline



3/17/20: 3 days prior to hospitalization

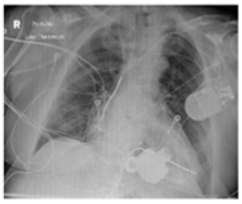


3/20/20: Hospital day 0
O2 requirement: 2 L./min via nasal cannula
Treatment: Hydroxychloroquine



3/22/20: Hospital day 2
O2 requirement: 50 L/min with FiO2 70%
via high flow nasal cannula
Treatment: Hydroxychloroquine

3/22/20: Intubation



3/23/20: Hospital day 3
O2 requirement: AC/VC with FiO2 60% and
PEEP 14 cmH2O
Treatment: Hydroxychloroquine stopped
due to QTc prolongation

3/24/20: Hospital day 4
O2 requirement: AC/VC with FiO2 60%
and PEEP 14 cmH2O
Treatment: Tocilizumab

3/28/20: Hospital day 8
Patient died.