Case Report

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COVID-19 Induced Cytokine Storm Manifesting as Takatsubo Cardiomyopathy and Sepsis Reversed with Therapeutic Plasma Exchange

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Abstract

The pathophysiology of severe COVID-19 involves a hyperactive immune response often referred to as cytokine storm. This pathway may lead to different clinical phenotypes including acute respiratory distress syndrome, sepsis, cardiomyopathy, and/or multiple organ failure. Therapeutic plasma exchange (TPE) has been proposed as adjunct treatment for sepsis and cytokine storm with case reports and small trials showing clinical success. We present a case of Takotsubo cardiomyopathy with refractory cardiogenic shock that reversed following TPE. Our patient subsequently developed sepsis and again responded clinically to TPE. This case offers an exciting anecdotal outcome while generating hypotheses for further clinical research.

Background

The pathophysiologic result of COVID-19 infection is complex and ranges from mild to severe disease. A process that plays a major role is the "cytokine storm" phenomenon which is essentially a hyperactive immune response similar to bacterial induced severe sepsis [1, 2, 3]. Many treatments have targeted specific components of this pathway with variable success. Therapeutic plasma exchange (TPE) has occasionally been used for sepsis, and clinicians first proposed TPE as a potentially useful intervention against severe COVID infection early in its history [4]. Mainly through case reports and series, clinicians have reported promising outcomes in COVID patients receiving TPE as part of their care [5, 6]. Indications have varied, most commonly for cytokine storm and sepsis, but also include a case of reverse Takotsubo cardiomyopathy successfully reversed after TPE.

Objective

To contribute to the growing experience using TPE, we present a case of severe COVID pneumonia complicated by acute respiratory distress syndrome (ARDS), sepsis, multiple organ failure, and Takotsubo cardiomyopathy successfully treated with adjunct TPE. The case received exemption from the Lexington Medical Center Institutional Review Board.

Case Report

A 74 year old female with history of hypertension and diabetes presented with shortness of breath for three days. SARS-CoV-2 PCR was positive. She was hypoxemic with saturations in the 40s. EKG showed ST segment elevation in the anteroseptal leads. She was intubated and taken to the cath lab where angiography noted patent coronaries with Takotsubo cardiomyopathy and an ejection fraction (EF) of 30%. She required high dose infusions of epinephrine, norepinephrine, and vasopressin so a temporary left ventricular assist device (LVAD) was placed and she was admitted to the ICU. Soon after admission she developed agonal respirations with mottled lower extremities to the torso and suffered asystolic cardiac arrest. She was made Do Not Resuscitate by family. When the LVAD was removed, she had return of pulses but remained hypotensive requiring epinephrine, levophed and vasopressin infusions. A pulmonary artery catheter (PAC) was placed and milrinone was added with persistent shock but she developed unstable supraventricular tachycardia and required electrical cardioversion and cessation of milrinone. She developed multiple organ failure and was initiated on continuous renal replacement therapy (CRRT). She was treated with all available therapies for COVID-19 including corticosteroids, tocizulimab, and treatment dose anticoagulation. With her ongoing clinical decline, TPE was initiated on hospital day three. Hemodynamics improved and she weaned off inotropes and vasopressors. She developed hypertension and was started on a continuous nicardipine infusion for hypertension. She remained on CRRT with aggressive volume removal. On hospital day nine she was liberated from mechanical ventilation. Repeat echocardio-

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Table 1: *Hemodynamic/cardiac parameters by hosptial day in relation to therapeutic plasma exchange.*

Hospital Day	PAS/ PAD	CO/CI	SVR	Ejection Fraction	Cardiac Drips
1	40/26	4.0/2.0	1578	30%	epi, norepi, vaso, mil
*4	26/16	5.4/2.6	903		none
9				67%	nicardipine
10					nicardipine
11					nicardipine
12					norepinephrine
*13					norepinephrine
*14					none

**Days of therapeutic plasma exchange*
PAS=pulmonary artery systolic pressure; PAD=pulmonary artery diastolic pressure; CO=cardiac output; CI=cardiac index; SVR=systemic vascular resistance; epi=epinephrine; norepi=norepinephrine; vaso=vasopressin; mil=milrinone

Table 2: *Biomarker profile by hosptial day in relation to therapeutic plasma exchange.*

Hospital Day	Ferritin	CRP	LDH	Ddimer	AST	ALT	WBC
1	7486	28.8					
2	4381	142		3566	592	391	
*3	3366		1106		355	368	
*4	784		736		180	219	
*5	727		742		132	157	
11	1769	13.7		1682			30.2
12	2219	10.3					29.3
*13			707				25.5
*14							26.5
31	446						
*Days of therapeutic plasma exchange							

**Days of therapeutic plasma exchange*
CRP=C-reactive protein; LDH=lactate dehydrongenase; AST=aspartate aminotransferase
ALT=alanine aminotransferase; WBC=white blood cell count

gram showed an EF of 67% (**Table 1**).

Following extubation she deteriorated with leukocytosis and elevated biomarkers suggesting cytokine storm and sepsis. She received another dose of tocizulimab and was started on broad antimicrobials for possible superimposed infection. Her hemodynamics worsened requiring low dose norepinephrine infusion. She was again treated with TPE and showed clinical improvement. She weaned off vasopressors and transitioned to low flow oxygen (**Table 1**, **Table 2**). She transferred out of ICU on day 19, last dialyzed on day 25, and thereafter recovered to pre-admission baseline. Her hospitalization was complicated further by lower extremity DVT and gastric stress ulcers. She was weaned off oxygen and was discharged to inpatient rehab on hospital day 41.

Discussion

In its most simple terms, sepsis is life threatening infection. Its pathophysiology is quite complex and not entirely understood, but results of targeted therapeutics have been largely disappointing. TPE offers a promising, less-targeted therapy, and a single prospective clinical trial demonstrated a trend toward improved survival with adjunct TPE in sepsis [7]. Others have reported similar favorable outcomes including improved survival and decreased need for vasopressor support [8]. Prior to COVID, our group considered TPE on a case to case basis for patients meeting ASFA criteria of sepsis with multiple organ failure, and retrospectively observed a favorable clinical response [9]. Given the shared pathophysiology, we postulated that TPE may play a role in certain cases of severe COVID-19 infection and began to utilize TPE on a case to case basis in March 2020 with some success [10].

Our patient is unique in that she manifested two separate shock states, both due to SARS-CoV-2 infection. Many of the earliest reports in COVID-19 describe cardiac involvement, presenting in various ways, although the pathophysiology is not entirely understood and is likely multifactorial. Notably, autopsy reports have not definitively confirmed myocarditis and most available data suggests that the acute myocardial depression is due to the profound inflammatory response [11]. Outside COVID, stress-induced cardiomyopathy has been shown to be the direct result of high levels of epinephrine on ventricular myocardium [12]. While several cases of self-resolving Takotsubo in the setting of COVID-19 have been reported, Faqihi reported a case of reverse Takotsubo cardiomyopathy in fulminant COVID-19 with cytokine storm that resolved following TPE [13]. Our patient's initial instability was due to refractory cardiogenic shock despite mechanical circulatory support (MCS), inotropic/vasopressor support, and CRRT. Her exam and PAC values demonstrated ongoing cardiogenic shock while laboratory values were consistent with hyperinflammation and coagulopathy consistent with cytokine storm. Extrapolating from the data above, we felt that she might benefit from TPE. Indeed, her hemodynamics quickly improved, inflammatory biomarkers decreased, and cardiac function returned to normal following TPE (**Table 1**). After her initial improvement, she again worsened with development of sepsis and multiple organ dysfunction. Again, her illness appeared to be driven by cytokine storm and after an additional round of TPE she improved clinically. While many laboratory values are missing/incomplete, the available biomarker response suggests abatement of the cytokine storm with TPE on both occasions (**Table 2**). These trends - both clinical and laboratory – add to the existing data associating cytokine storm with severe illness, and a potential role for TPE.

Despite the temporal relationship to TPE, it is impossible to know whether our patient would have improved without TPE.

Furthermore, the sepsis that subsequently developed after the initial TPE may have been result of the net response to TPE originally. Some clinicians have expressed concern about the possible net negative immunologic effects of TPE [14], and certainly this cannot be refuted or proven in our case. While safety of TPE in sepsis has been reported, the net effect of treatment should be investigated in a prospective manner to standardize monitoring and safety. Additionally, clinical features and/or laboratory values that suggest cytokine storm are highly variable. Threshold abnormalities for certain markers have been associated with poor outcomes [15], but the clinical impact of various treatments including TPE is uncertain. It is also unclear whether decreases in these values signifies clinical improvement and "successful" use of said treatments.

A case report in real time is limited and should not be used to change clinical practice but these results should be noted. As SARS-CoV-2 continues to mutate, critical illness is certain to some degree. Targeted therapies are likely to evolve and change with time, but TPE may continue to offer a temporizing intervention that may prevent host-mediated damage in response to infection. While the significance of the biomarker trend is uncertain, the favorable hemodynamic response has been demonstrated rather consistently and may be particularly useful in the case of catecholamine induced stress cardiomyopathy. Our case offers an exciting anecdotal outcome while generating hypotheses for further clinical research.

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