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Abstract: COVID-19 morbidity and mortality are not equivalent to other etiologies of acute respiratory distress syndrome (ARDS) as fulminant activation of coagulation can occur, thereby resulting in widespread microvascular thrombosis and consumption of coagulation factors. A 53-year-old female presented to an emergency center on two occasions with progressive gastrointestinal and respiratory symptoms. She was diagnosed with COVID-19 pneumonia and admitted to a satellite intensive care unit with hypoxemic respiratory failure. She was intubated and mechanically ventilated, but her ARDS progressed over the next 48 hours. The patient was emergently cannulated for veno-venous extracorporeal membrane oxygenation (V-V ECMO) and transferred to our hospital. She was in profound shock requiring multiple vasopressors for hemodynamic support with worsening clinical status on arrival. On bedside echocardiography, she was found to have a massive pulmonary embolism with clot-in-transit visualized in the right atrium and right ventricular outflow tract. After a multidisciplinary discussion, systemic thrombolytic therapy was administered. The patient’s hemodynamics improved and vasopressors were discontinued. This case illustrates the utility of bedside echocardiography in shock determination, the need for continued vigilance in the systematic evaluation of unstable patients in the intensive care unit, and the use of systemic thrombolytics during V-V ECMO in a novel disease process with evolving understanding. Key Words: COVID-19, pulmonary embolism, ECMO, thrombolysis, blood clot.

There are many reasons that COVID-19 morbidity and mortality are not parallel to other etiologies of acute respiratory distress syndrome (ARDS). One of the main reasons is that COVID-19 patients have dysregulated coagulation parameters. Patients with severe COVID-19 infection can become coagulopathic with fulminant activation of coagulation, resulting in widespread microvascular thrombosis and consumption of coagulation factors (1). Specifically, patients with high D-dimer levels have increased mortality when compared to patients with lower D-dimer levels (2). Additionally, there is a risk stratification for patients who may need systemic anticoagulation compared to prophylactic doses of heparin, especially in patients who have met the sepsis-induced coagulopathy (SIC) criteria (40.0% vs. 64.2%, p = .029) compared to those with an SIC score <4 (29.0% vs. 22.6%, p = .419), or with markedly elevated D-dimer levels (>6 fold at the upper limit of normal) (3,4).

Similar to severe cases of influenza, severely ill COVID-19 patients may have dysregulated immune systems, initially favoring a hyperimmune response (5). We describe the diagnosis and management of obstructive shock secondary to massive pulmonary embolism (PE) in a patient with COVID-19 supported on veno-venous
extracorporeal membrane oxygenation (V-V ECMO). With bedside ultrasound assessment, we learned that she had a previously unsuspected massive PE. We describe the use of systemic thrombolytic therapy in this clinical scenario.

CASE

A 53-year-old, African-American female presented to the local emergency center (EC) with a 3-day history of numbness in bilateral lower extremities, generalized weakness, and fever (102.3°F). Her body mass index was 40.4 kg/m², and her chest x-ray (Figure 1, day 1) and basic laboratory studies were unremarkable; she was discharged home. She returned with symptoms of generalized weakness, nausea, vomiting, dry cough, and dizziness. Her oxygen saturation was 93%, and she had a fever (102.3°F). Her blood work was notable for hyponatremia, transaminitis (92 units/L alanine aminotransferase; 100 unit/L aspartate transaminase), and a white blood cell (WBC) count of 3,500 with 19.8% lymphocytes. An electrocardiogram (ECG) revealed a heart rate of 97 beats per minute with a Q wave and inverted T wave in lead III. The chest x-ray revealed mild bilateral interstitial prominence (Figure 1, day 3). A COVID-19 nasopharyngeal swab test was positive, and she was sent home to isolate and recover; she was asked to return if her symptoms worsened.

She was hospitalized at a satellite hospital 4 days later with acute respiratory distress. She had arrived via ambulance with an oxygen saturation of 75% on room air. Upon arrival at the EC, she had a low-grade fever (99.9°F) and was tachycardic (127 beats per minute) with a respiration rate of 37 and 89% saturation on 100% non-rebreather. She was subsequently intubated, mechanically ventilated, and admitted to the intensive care unit (ICU). Her labs had not significantly changed from the prior EC visit. Of note, her B-type natriuretic peptide level was 17 pg/mL and troponin was <.02 ng/mL. Her WBC count was now 6,100 with 13.8% lymphocytes. A coagulation profile was not checked upon admission. An ECG revealed sinus tachycardia. A chest x-ray revealed an enlarged cardiac silhouette with interstitial pulmonary opacities (Figure 1, day 6).

Case Progression

Despite intubation and mechanical ventilation, her hypoxemic respiratory failure required increased positive end-expiratory pressure (PEEP). She was started on empiric intravenous antibiotics, prophylactic doses of subcutaneous enoxaparin, and managed with sedatives as well as ceftriaxone, hydroxychloroquine, azithromycin, and oseltamivir. She progressively required high-dose sedation with fentanyl, midazolam, and therapeutic paralysis with cisatracurium. Given her progressive refractory hypoxemic respiratory failure, she was also started on manual prone position therapy. She was continued on lung-protective ventilation with VT 375 mL, respiratory rate 24 breaths per minute, PEEP 18 cm H₂O, and FiO₂ of 100%. With this, her compliance was 29 cm H₂O and mean airway pressure was 23.

On hospital day 2, she was started on low-dose norepinephrine and continued prone position therapy. Laboratory investigations included worsening respiratory acidosis, D-dimer > 20, erythrocyte sedimentation rate of 84, and leukocytosis with 2.1% lymphocytes. Her P/F ratio was 115. On hospital day 3, a mobile ECMO team was dispatched via air ambulance. The patient received a heparin bolus of 88.49 units/kg before ECMO cannulation. The patient was on V-V ECMO using the Cardiohelp HLS Set Advanced 7.0 System (Getinge, Wayne NJ) via a 19 French single-stage (Medtronic, Minneapolis, MN) right common vein and a 23 French multistage (Medtronic) left common femoral vein cannulation approach. Following cannulation, the patient was noted to have worsening

Figure 1. Chest x-ray views. These images show the progression of the disease from presentation to an outside hospital to the current hospitalization from day 1 to day 9.

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shock requiring escalating doses of vasopressors during transport to the hub hospital.

Upon arrival, she was hypotensive, and intravenous crystalloid and colloids were given with the differential diagnosis of hypovolemic vs. vasoplegic shock. An immediate point-of-care ultrasound was done to confirm optimal cannula position. A bedside echocardiogram revealed multiple clots in transit through the right ventricle with right ventricular (RV) dilatation (Figure 2).

The decision was made to administer thrombolytics in the ICU. Other treatment options were dismissed given her COVID-19 status. The initial coagulation study after ECMO cannulation showed a therapeutic activated partial thromboplastin time (aPTT) of 97 seconds, an international normalized ratio (INR) of 1.64, and thrombin elevated at 28 seconds with a high normal fibrinogen level of 441 mg/dL, all consistent with adequate anticoagulation effect. Fifty milligrams of alteplase were given as an infusion over a 2-hour period. During this infusion, the heparin drip was held. Four hours after alteplase infusion was completed a repeat coagulation study showed an aPTT of 50 seconds, an INR of 1.8, thrombin decreased to 19 seconds, and fibrinogen decreased to 370 mg/dL. A thromboelastography study was also performed at the same time, and all values were within the reference range indicating an adequate balance between hemostasis and coagulopathy. A heparin infusion was restarted afterward at 18 units/kg/h for a goal aPTT of 70–90 seconds.

Continuous renal replacement therapy was initiated for anuric acute renal failure. The patient gradually attained hemodynamic stability, no longer requiring vasopressors, and within 18 hours her lactic acid normalized. A repeat echocardiogram 36 hours after thrombolytic administration shows a 1.4 cm mobile thrombus still present in the right ventricle. She continued to receive V-V ECMO support with full ICU management in place. Notably, her initial interleukin-6 level was very elevated at 1,092.4 pg/mL. Due to the patient necessitating deep sedation and therapeutic paralysis, computed tomography of the brain was obtained.

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<th>Table 1. Potential therapeutic options.</th>
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ECMO, extracorporeal membrane oxygenation; MAP, mean arterial pressure; RV, right ventricular; VA-V ECMO, veno-arterio to venous extracorporeal membrane oxygenation.

Figure 2. Transthoracic echocardiograms. These images reveal an RV thrombus in the PLAX view and the subcostal view. The ECMO return cannula is seen in the IVC. ECMO, extracorporeal membrane oxygenation; IVC, inferior vena cava; PLAX, parasternal long axis; RV, right ventricular.
was found to be normal, without evidence of intracerebral hemorrhage. Unfortunately, there was no recovery in lung function, and the patient was not deemed to be a lung transplant candidate. The patient expired at day 41 of hospitalization.

CONCLUSIONS

The management of obstructive shock secondary to massive PE while supported on V-V ECMO is not well described. Patients previously supported on V-V ECMO have a 71.4% chance of cannula-associated deep vein thrombosis despite therapeutic aPTT (6). In our patient, the D-dimer was >20 after V-V ECMO cannulation at the time of transfer, and she was given systemic heparin. Acute RV failure from increased pulmonary vascular resistance is frequently associated with ARDS itself, hypoxia and hypercapnia, and/or high airway pressures from mechanical ventilatory support (7). Miranda et al. were able to show a decrease in mean pulmonary artery pressures and improvement in cardiac indexes with the use of V-V ECMO (8). Strategies include escalating anticoagulation to a higher aPTT, changing to bivalirudin, or considering thrombolytics. These strategies have not been well studied either individually or together. Due to the patient’s rising lactate, increasing vasopressor/inotropic requirement, and imminent cardiopulmonary arrest, a more immediate and definitive therapy was needed. Three therapeutic options along with the benefits and risks are summarized in Table 1. We evaluated our patient for percutaneous intervention; however, early in the pandemic, coronavirus transmission was not yet fully understood. We opted against transferring the patient to the cardiac catheterization laboratory for suction or mechanical thrombectomy. In addition, the patient remained in a hypercoagulable state despite receiving therapeutic doses of anticoagulation; therefore, we were reluctant to escalate to mechanical circulatory support via veno-arterio to venous ECMO.

Although there are no large randomized studies evaluating the efficacy of systemic thrombolytics in unstable PE, a few studies have demonstrated early hemodynamic improvement (9,10) and a reduced odds ratio of short-term all-cause mortality (OR 0.69; 95% CI 0.49–0.95) (11). However, the significant trade-off of systemic thrombolysis is potential uncontrolled systemic or local bleeding. Studies have quoted an intracranial hemorrhage rate of up to 4% (12), but the risk in patients on V-V ECMO support for COVID is truly unknown. Our patient was already on systemic unfractionated heparin infusion, so only 50 mg of alteplase was administered. No significant bleeding, including at ECMO cannula sites, was immediately observed. Frequent and extended panel coagulation tests were performed after thrombolytic administration to ensure an adequate balance between thrombotic and bleeding parameters and to detect any unexpected events related to thrombolytics in the presence of ECMO.

As previously mentioned, within the next 24 hours after administration of alteplase, her vasopressor and inotropic requirements significantly improved. An echocardiogram 36 hours after thrombolytic administration showed only a 1.4 cm RV thrombus, which resolved on repeat imaging 15 days later.

One should be vigilant to include thrombosis in the differential diagnosis of COVID-19 patients that are in shock. Given the widespread availability of bedside ultrasound and specifically, bedside echocardiography, a detailed approach to image-guided differential diagnosis management of the patient in shock on or off ECMO is now recommended.

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REFERENCES