Case Report

Limb Ischemia due to Extensive Arterial Thrombosis in the Absence of Venous Occlusion as an Unusual Complication of Critical Illness from COVID-19

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Keywords

Arterial thrombosis · COVID-19 · Thromboembolism · Thrombophilia · Ischemia

Abstract

There is increasing evidence of a link between the coronavirus disease 2019 (COVID-19) and venous and arterial thrombotic events. Here, we report a 60-year-old male patient with severe COVID-19 who developed extensive arterial thromboses and limb ischemia despite being on therapeutic-dose anticoagulation. While the exact mechanism for such events is unknown, our report highlights the importance of maintaining a high degree of suspicion in critically ill patients. Further research should focus on the mechanistic pathways along with the optimal anticoagulation and/or antithrombotic strategy.

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Introduction

The respiratory disease from coronavirus disease 2019 (COVID-19) has caused over 36 million confirmed infections globally with over 1 million deaths as of October 2020 [1]. Extra-pulmonary complications of COVID-19 are increasingly reported in the literature, including hypercoagulable state and thromboembolic events [2]. Current recommendations for thrombosis prophylaxis in hospitalized COVID-19 patients do not differ from other hospitalized patients and current National Institute of Health guidelines do not recommend anticoagulation prophylaxis to prevent arterial thromboses outside of the usual standard of care for patients without COVID-19 [3]. Additionally, there are no recommendations for using markers of coagulopathy to guide treatment, despite some evidence pointing towards a benefit for patients with a higher D-dimer level [4]. As our knowledge of coagulopathy in COVID-19 is developing, different clinicians and institutions may choose different strategies of anticoagulation using prophylactic dose, intermediate dose, or even full therapeutic dose. Here, we report a case of extensive arterial, but not venous, thrombosis leading to limb ischemia and eventual demise of a patient with COVID-19. Publication consent was obtained from a family member.

Case Presentation

A 60-year-old Asian-American male with a past medical history of hypertension, hyperlipidemia, diabetes mellitus, chronic lymphocytic leukemia, deep venous thrombosis (DVT), bacterial pneumonia 7 years prior complicated with acute respiratory distress syndrome (ARDS) with prolonged ventilator dependence, right-sided pneumothorax requiring chest tube insertion and subsequent video-assisted thoracoscopic wedge resection of the left lower lobe of the lung, decortication, right pleurectomy and pleurodesis, presented to the emergency room with complaints of fever, cough, and shortness of breath for 7 days. He never smoked cigarettes, and despite extensive pulmonary comorbidities, was functionally independent and active prior to the onset of symptoms. He did not report traveling recently, his wife had similar symptoms, and they were both self-monitoring symptoms including oxygen saturation checks. He noticed a nadir oxygen saturation of 80% on the day of the emergency room visit. In the emergency room, he was noted to be alert and oriented, with mild respiratory distress, bilateral rales on auscultation, speaking in full sentences. His vital signs were a blood pressure of 111/69 mm Hg, heart rate of 86 beats per minute, respiratory rate of 24 per minute, oral temperature of 98.4 F, and oxygen saturation of 87% while sitting up, and responding to 3 L of supplemental oxygen via nasal cannula to 96%. The patient's emergency room workup included a polymerase chain reaction (PCR) test for COVID-19 which was negative. A CT-scan of the chest revealed bilateral airspace opacities consistent with viral pneumonia. The patient was admitted to a COVID-19 ward in isolation. An ECG on admission showed normal sinus rhythm. He was found to have mild hyponatremia which was attributed to decreased oral intake. The rest of his lab values can be found in [Table 1](#).

Symptomatic therapy including inhaled bronchodilators, antipyretics, and cough suppressants as needed was started. Additionally, incentive spirometry, deep breathing exercises,

and self-proning were implemented. The patient was not on anticoagulation as an outpatient. Enoxaparin 0.5 mg/kg prophylactic dose was initiated. He was also prescribed his outpatient medications including metformin, atorvastatin, and losartan. The pulmonary and infectious disease services were consulted, and based on their recommendations, hydroxychloroquine 800 mg initial dose with 400 mg for 4 days with close monitoring for QT prolongation was started. A repeat chest X-ray on day 2 of admission showed diffuse airspace opacity, and a repeat PCR test for COVID-19 was sent which was negative. On hospital day 3, the patient's oxygen requirements increased to 10 L/min via non-rebreather mask. In response to this worsening respiratory function, the pulmonary service recommended methylprednisolone 1.5 mg/kg in 3 divided doses, which was given. On day 4, continuous proning and 100% supplemental oxygen were required to maintain oxygenation above 91%. After consultation with the infectious disease service, the patient was started on a 3-day course of anakinra. Given the increased D-dimer and clinical worsening, he was transitioned to the full therapeutic dose of enoxaparin 1 mg/kg twice a day. An anti-factor Xa level of 0.93 IU/nL showed therapeutic response (Table 1). A PCR test for COVID-19 was sent for the third time on day 5 which returned positive. His clinical status was stable after these interventions.

On day 9 of admission, he was emergently intubated. Upon arrival to the intensive care unit (ICU), his vital signs were a blood pressure of 100/58 mm Hg, heart rate of 99 bpm, respiratory rate of 30/min, oxygen saturation of 94%, and rectal temperature of 99.1 F. On physical examination, the patient was sedated and paralyzed, with bilateral equal breath sounds on auscultation. Mechanical ventilation was initiated according to the lung protective ventilation strategy recommended by ARDSnet [5]. He was sedated with fentanyl, propofol, and ketamine infusions. On day 1 of ICU admission, the patient was treated for hyperkalemia. Later that day, the patient was started on an infusion of vasopressin for persistent hypotension with mean arterial pressure (MAP) below 65 mm Hg, while the positive end-expiratory pressure was minimized to 8 (with plateau pressures measured at 29 cm H₂O). An insulin infusion was also started for persistent hyperglycemia. Within 12 h, the patient required an infusion of norepinephrine which was titrated to 0.12 µg/kg/min to maintain MAP above 65 mm Hg, while propofol and fentanyl infusions were titrated down to mitigate their depressive cardiovascular effects. The urine output was maintained at 0.5 cc/kg/h during this period. His arterial gas showed compensated respiratory acidosis. The insulin drip was subsequently stopped, and his norepinephrine infusion was weaned down to 0.07 µg/kg/min. On day 2, he was given an intravenous bolus of furosemide 20 mg to maintain a neutral fluid balance. His serum creatinine remained stable.

On the morning of the third day of ICU admission, the lower extremities were noted to be cold to touch. Dorsalis pedis and posterior tibialis pulses were absent on palpation. Doppler signal was only detected in the popliteal arteries. The left lower extremity on repeat exam 1 h later was noted to be mottled, with all pulses below the knee absent. Shortly after, the right lower extremity was also noted to be mottled. A stat loading dose of aspirin 325 mg was given enterally, enoxaparin was discontinued, and unfractionated heparin infusion was started. Emergent vascular surgery consultation was called, and duplex ultrasound studies of arterial and venous phases were performed emergently. Despite attempts at weaning the

vasopressors, the norepinephrine dose after the onset of signs of limb ischemia peaked at 0.09 µg/kg/min.

The duplex ultrasound showed no DVT on the venous phase, and the arterial phase showed an occlusion proximal to the short segment of the distal right external iliac artery, with a velocity of 38 cm/s. The right common femoral artery was noted to be patent with marked tardus parvus waveform abnormality and a velocity of 13 cm/s. The right deep femoral artery was occluded. The right superficial femoral artery was patent with low-velocity tardus parvus waveforms with velocity ranges from 12 to 24 cm/s. The right popliteal, tibio-peroneal trunk, posterior tibial, peroneal artery, and dorsalis pedis were all occluded. No arterial blood flow was demonstrated in the left lower extremity arteries (Fig. 1). Upon consultation with the vascular surgery service and discussing with the patient's family, a decision was made to proceed with intravenous tissue plasminogen activator (alteplase 0.5 mg/kg) therapy, as the patient had increased vasopressor requirements, with norepinephrine at 0.28 µg/kg/min. The patient was challenged with an intravenous bolus of lactated ringer with minimal response. After discussions with the patient's family and due to poor response to therapies, they opted for comfort measures. The patient expired prior to the completion of his alteplase infusion, and the family did not request an autopsy.

Discussion

Here, we presented an unusual case of COVID-19 infection with an initial stable period and a rapid deterioration leading to ICU admission, and eventual demise due to extensive arterial thrombosis. There are several possible explanations for the patient's poor outcome, including a history of prior DVT, presumed hypercoagulable state of acute illness, platelet hyperreactivity, direct thrombogenic effects of COVID-19 infection, breakthrough thrombosis, disseminated intravascular coagulation (DIC), cytokine storm, endothelial dysfunction, activation of the renin-angiotensin-aldosterone pathway, and undetected overwhelming infection [6–10].

Based on existing guidelines [11], patients hospitalized with acute illness receive chemoprophylaxis against venous thromboembolism (VTE). However, some studies suggest that even with appropriate prophylaxis, the rate of thrombosis is still 6–11% [12]. This patient was not on anticoagulation prior to presentation, since his DVT was in the setting of critical illness, 7 years prior.

Evidence is mounting on the thrombogenic effects of COVID-19, with cases reported with venous and arterial thromboses [13, 14] and one observational study showing increased incidents of acute limb ischemia compared to the same period last year [15].

One case series of autopsies of COVID-19 patients found thrombotic microangiopathy [16]. While our patient did have a sudden increase of D-dimer during his hospital stay, he was promptly transitioned to therapeutic dose anticoagulation with a subsequent decrease in D-dimer levels (Table 1). While there has been much discussion regarding the presence of DIC in COVID-19, this patient's physical examination and laboratory results did not support a diagnosis of DIC.

There are few reports of extensive arterial thrombosis in COVID-19 patients. Previously, Klok et al. [17] reported a case series of venous and arterial thromboembolism in ICU patients with COVID-19. Zhang et al. [18] described 3 cases of limb ischemia with COVID-19 who were tested positive for anticardiolipin and anti-beta2 glycoprotein I but not lupus anticoagulant. Helms et al. [19] describe a 62-year-old patient who developed acute limb ischemia without digital necrosis or purpura. Merz et al. [20] reported a 70-year-old female with no history of thrombosis or hypercoagulopathy, presenting with extensive arterial thrombosis. Vacirca et al. [21] reported a distal thrombosis of the abdominal aorta and anterior and posterior tibial arteries in an intubated 58-year-old female with COVID-19 and no previous medical history other than hypertension. Kaur et al. [22] reported a patient with right upper limb ischemia due to extensive thrombosis. Baccellieri et al. [23] reported a patient with COVID-19 and extensive lower limb thrombosis with concurrent heparin resistance who was previously healthy. A recent systematic review has gathered previous reports of arterial thrombosis [13]. The optimal antithrombotic prophylactic regimen for patients with severe COVID-19 infections remains to be established. Although most organizations recommend standard-dose anticoagulation prophylaxis, some experts have suggested using higher doses, and high-quality trials to address this question are warranted. Currently, there are some ongoing clinical trials, the results of which will help to optimize the prevention strategy [24]. These reports highlight the risk of thrombosis in COVID-19 patients with potentially lethal outcomes, even in the absence of venous thrombosis, as in our case. We add to the current body of evidence by reporting a case with extensive arterial thrombosis, without evidence of any venous thrombosis, while already receiving therapeutic-dose anticoagulant therapy.

Conclusion

Arterial thrombosis in the absence of VTE is not a common presentation of COVID-19, which requires a high degree of suspicion in a patient with early signs of limb ischemia. Prompt recognition of this condition may prevent devastating sequelae such as limb amputation and death.

Statement of Ethics

Written informed publication consent and any accompanying images were obtained from the patient's daughter post-mortem.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.N., M.A.B. and D.J. were responsible for conception and design, analysis and interpretation, writing the manuscript, and critical revision of the manuscript. D.J. was responsible for collecting the data. All authors reviewed the final draft and approved the final manuscript.

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Fig. 1. Doppler ultrasound showing occlusion of the right external iliac artery (a), occlusion of the right deep femoral artery (b), occlusion of the right popliteal artery (c), and complete absence of flow in the left common femoral artery (d).

Table 1. Laboratory trends of the patient during admission

	Normal range	Day 1 admission	Day 9 Day 1 ICU	Day 10 Day 2 ICU	Day 2 ICU 12 h	Day 11 Day 3 ICU
WBC	3.8–10.5 K/uL	5.42	22.08	18.7		18.4
Hemoglobin	13–17 g/dL	14.7	14.6	13.9		13.3
Hematocrit	39–50%	45.4	46.8	46.4		41.7
Platelets	150–400 k/uL	271	295	159		214
Neutrophils	1.8–7.4 K/uL	3.69				13.9
Lymphocytes	1–3.3 K/uL	0.89				1.29
ESR	<20 mm/h	120	59			
D-Dimer	<228 ng/mL DDU	209	13,993	35,715		2,351
Fibrinogen	<350 mg/dL					
aPTT	27.5–36.3 s	36.7	32.8	37.4		
PT	10–12.9 s	12.8	13.7	14		
INR	0.88–1.16	1.11	1.19	1.22		
Anti-factor Xa	0.5–1.1 IU/mL				0.93	
Arterial lactate		1.7 (venous)	6.1	2.6	2.1	1.8
BUN	7–23 mg/dL	15	25	29	22	23
Creatinine	0.5–1.3 mg/dL	0.8	0.72	0.7	0.6	0.61
Total protein	6–8.3 g/dL	8.2	6.3	6.2		6.1
Albumin	3.3–5 g/dL	3.7	2.8	2.8		2.7
T bili	0.2–1.2 mg/dL	0.5	0.8	0.4		0.7
Alk P	40–120 U/L	49	263	179		139
AST	10–40 U/L	39	37	31		148
ALT	10–45 U/L	41	84	66		76
Troponin T	<50 ng/L		78			
CRP	<0.4 mh/dL	13.83				
Ferritin	30–400 ng/mL	3,374				
CD3 %	59–83%		64			
CD3 count	672–1,870 μ L		230			
CD4 %	30–62%		45			
CD4 count	489–1,457 μ L		167			
CD8 %	12–36%		17			
CD8 count	142–740 μ L		62			
CD4/CD8 ratio	0.9–3.6		2.69			

Alk P, alkaline phosphatase; ALT, alanine transferase; aPTT, activated prothrombin time; AST, aspartate transferase; BUN, blood urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; INR, international normalized ratio; PT, prothrombin time; WBC, white blood cells; T bili, total bilirubin.