Acute limb ischemia as sole initial manifestation of SARS-CoV-2 infection

Owen Thompson, MD,[a] Damon Pierce, MD,[b] Dennis Whang, MD,[a] Meaghan O'Malley, MD,[c] Bob Geise, MD,[d] *and* Uma Malhotra, MD,[d,e] *Seattle, Wash*

ABSTRACT

We present the case of a patient with acute upper limb ischemia as the sole initial manifestation of severe acute respiratory syndrome associated with coronavirus disease 2 infection, without concomitant respiratory symptoms or pneumonia. Viral infection presumably precipitated the patient's thromboembolic event, causing multifocal vascular occlusions. This case illustrates that coronavirus disease-19 must be considered in the differential diagnosis of patients presenting with signs or symptoms of coagulopathy, even in the absence of respiratory symptoms. We believe that an awareness of the variety of clinical presentations in patients with coronavirus disease-19, particularly extrapulmonary manifestations, is critical for optimal patient management as well as implementation of appropriate infection prevention measures. (J Vasc Surg Cases and Innovative Techniques 2020;6:511-3.)

Keywords: COVID-19; SARS-CoV-2; Limb ischemia; Arterial thrombosis; Coagulopathy

Since the emergence of coronavirus disease-19 (COVID-19) in late 2019, widespread attention has been directed to coagulopathies associated with this novel viral illness. Early studies from China reporting on the characteristics of COVID-19 noted an association between D-dimer elevation and a poor prognosis.[1,2] Subsequent studies of hospitalized patients with COVID-19 have noted increased venous thromboembolic events in more severe disease, with one study noting venous thromboembolic events in 16.7% of critically ill cases, compared with only 6.4% in the general wards.[3-5] Anticoagulant treatment in severe cases is associated with decreased mortality,[6] and multiple consensus statements have now been issued regarding both treatment and prophylaxis of thromboembolic disease in patients with varying disease severity.[7]

There are emerging reports of arterial thromboembolic disease as well. Klok et al[4] estimated a prevalence of arterial thrombotic events to be 3.7% (95% confidence interval, 0%-8.2%) among 184 patients in the intensive care unit, all of which were ischemic strokes. Lodigiani et al[3] identified strokes in 6.3% of intensive care unit patients vs 1.9% in the general wards. Cases of arterial thrombosis in the extracerebral circulation, including the aorta, pulmonary, and renal arteries, have been reported in critically ill patients.[8-10] More recently, five relatively young patients presenting with large vessel ischemic stroke were reported to have severe acute respiratory syndrome associated with coronavirus disease 2 (SARS-CoV-2) infection.[11]

Here we report a case in which a patient presented with acute limb ischemia and was found to have SARS-CoV-2 infection by surveillance testing many days before developing mild viral respiratory symptoms. The patient consented to the publication of the details and images related to the case.

CASE REPORT

A 42-year-old woman with type 2 diabetes mellitus and rheumatoid arthritis presented to the emergency department in a rural hospital with 5 days of right upper extremity pain, loss of sensation, and discoloration of her hand. Physical examination was significant for cyanosis of the right hand from fingertips to palm, absent sensation in several fingers, and 4/5 strength in the right hand. She denied any cough, dyspnea, fever, chills, rigors, myalgias, headache, sore throat, or anosmia. Laboratory tests showed a normal white blood cell count without lymphopenia. A computed tomography angiogram demonstrated a large thrombus in the proximal right subclavian artery immediately distal to the origin of the common carotid artery, as well as complete occlusion of the ulnar artery in the antecubital fossa extending to the hand (Fig). A chest radiograph showed no acute abnormalities. The patient was started on a heparin infusion and transferred to our institution for urgent surgical evaluation.

Upon admission, the patient underwent screening for SARS-CoV-2 by nasopharyngeal swab, recently instituted for all new patient admissions at our hospital. The test returned as positive and she was transitioned to full airborne precautions in advance

From the Department of Medicine,[a] Department of Vascular Surgery,[b] Section of Hematology Oncology,[c] and Section of Infectious Diseases,[d] Virginia Mason Medical Center; and the Department of Medicine, University of Washington School of Medicine.[e]

Author conflict of interest: none.

Correspondence: Uma Malhotra, MD, Infectious Diseases, Virginia Mason Medical Center, 1100 9th Ave, Seattle 98101, WA (e-mail: uma.malhotra@vmmc.org).

The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2468-4287

https://doi.org/10.1016/j.jvscit.2020.07.017

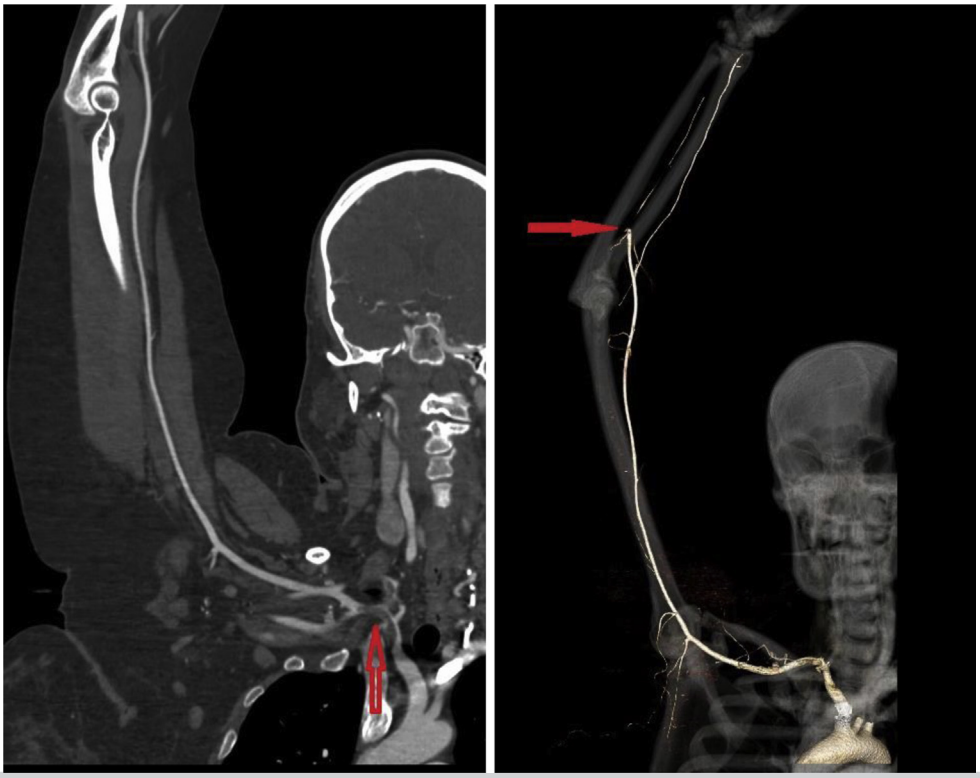

Fig. Multifocal vascular occlusions. Computed tomography angiogram of the right upper extremity demonstrating a large thrombus in the proximal right subclavian artery immediately distal to the origin of the common carotid artery (*left*), as well as complete occlusion of the right ulnar artery in the antecubital fossa and extending to the hand (*right*).

of her urgent operation. She underwent selective right brachial and ulnar artery embolectomy as well as subclavian artery embolectomy by open brachial incision. Right common carotid isolation and embolectomy was concomitantly performed for cerebral protection from embolization by open carotid incision. Powered air purifying respirators along with standard protective gear were used by all team members throughout the operation. She regained palpable radial and ulnar arteries in the affected extremity upon completion. On hospital day 2, she was transitioned from heparin to apixaban.

Over the subsequent days, the patient's fingers and palm showed steady improvement in circulation. In the setting of active anticoagulation, a modified evaluation for hypercoagulable state was done, checking for anti-B2-glycoprotein antibodies, prothrombin 20210 mutation, and factor V Leiden, all of which were normal. Staclot LA assay was negative, suggesting that lupus anticoagulant was likely negative. Notably, the patient was not on any hormonal therapy.

On hospital day 5 and 10 days from the initial onset of symptoms the patient developed mild hypoxia with an O_2 saturation of 92% on room air, prompting a computed tomography pulmonary angiogram, which demonstrated right middle lobe nodular/ground glass opacities characteristic of viral pneumonia. Additional studies included an elevated IL-6 of 34 pg/mL (reference value, <6 pg/mL), C-reactive protein of 27.8 mg/L (reference value, <8 mg/L), and a normal ferritin of 173 ng/mL. A repeat nasopharyngeal swab was again positive for SARS-CoV-2. On hospital day 6, the patient was initiated on intravenous remdesivir, a broad antiviral drug, as a part of a clinical trial. The drug is a nucleotide analog inhibitor of RNA-dependent RNA polymerase, with antiviral activity against several RNA viruses including, SARS and MERS. Patient was also given convalescent plasma. Her hypoxia rapidly resolved, and she was discharged home on day 9. At follow-up several days after discharge, the patient was noted to be at risk for middle digit tip loss presumably owing to microemboli to the digital arteries. At that visit, her lupus anticoagulant was confirmed to be negative.

DISCUSSION

Here we report the case of a patient in whom the only presenting manifestation of SARS-CoV-2 infection was acute limb ischemia secondary to thromboembolic arterial occlusion. The classic differential diagnosis for this presentation would include embolization of a cardiac or aneurysmal thrombus, or thrombophilic states such as are seen in antiphospholipid antibody syndrome, malignancy, or heparin-induced thrombocytopenia. A cardioembolic source was felt to be unlikely in our patient given the large clot size and the absence of any clinical suggestion of endocarditis, arrhythmia, or congestive heart failure. Similarly, her clinical presentation,

laboratory tests, and chest imaging did not suggest the presence of a malignancy; once the diagnosis of COVID-19 was made, further workup along these lines was not pursued.

Coagulopathy in the setting of COVID-19 is now widely acknowledged and may predispose to arterial thrombosis, possibly via elevations in antiphospholipid antibodies and/or lupus anticoagulant,[8,12] although these measures were not elevated in our patient. Systemic proinflammatory cytokine responses during SARS-CoV-2 infection may also induce the expression of procoagulant factors. Finally, angiotensin-converting enzyme 2, the receptor for SARS-CoV-2, is expressed on the membrane of vascular muscle and endothelial cells, and infection of these cells may induce an inflammatory response in the blood vessel walls, predisposing to clot formation.

SARS-CoV-2 infection may be the ultimate precipitant in a patient with other potential risk factors for thrombosis as perhaps in our case. Emerging reports of vascular skin findings in patients with COVID-19 also raise the possibility that infection may present with the sequelae of a virally induced hypercoagulable state, potentially preceding or in the absence of concomitant respiratory symptoms. Infection may also unmask a hypercoagulable state in patients with prior risk factors such as diabetes, which contributes to endothelial dysfunction and enhanced platelet activation.

In healthcare systems where screening is selectively offered based on presenting symptoms, we suggest expanding the criteria to include those with thromboembolic disease even in the absence of any other defining symptoms of COVID-19. Because expanded testing improves our understanding of the full epidemiology and protean manifestations of the disease, it is likely that patients with a variety of atypical manifestations of COVID-19 will be identified, including further cases of arterial thrombosis. We believe that awareness of the variety of clinical presentations in patients with COVID-19, particularly extrapulmonary manifestations, is critical both for optimal patient management and implementation of appropriate infection prevention measures.

REFERENCES

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
2. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020;18:844-7.
3. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Thromb Res 2020;191:9-14.
4. Klok FA, Kruip MJHA, Van der meer NJM, Arbous MS, Grommers DAMPJ, Kant KM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145-7.
5. Marone EM, Rinaldi LF. Upsurge of deep venous thrombosis in patients affected by COVID-19: preliminary data and possible explanations. J Vasc Surg Venous Lymphat Disord 2020;8:694-5.
6. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020;18:844-7.
7. Oudkerk M, Büller HR, Kuijpers D, van Es N, Oudkerk SF, McLoud TC, et al. Diagnosis, prevention, and treatment of thromboembolic complications in COVID-19: report of the National Institute for Public Health of the Netherlands. Radiology 2020:201629.
8. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl J Med 2020;382:e38.
9. Le berre A, Marteau V, Emmerich J, Zins M. Concomitant acute aortic thrombosis and pulmonary embolism complicating COVID-19 pneumonia. Diagn Interv Imaging 2020;101:321-2.
10. Lushina N, Kuo JS, Shaikh HA. Pulmonary, cerebral, and renal thromboembolic disease associated with COVID-19 infection. Radiology 2020:201623.
11. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoriah H, Singh IP, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. N Engl J Med 2020;382:e60.
12. Harzallah I, Debliquis A, Drénou B. Lupus anticoagulant is frequent in patients with Covid-19. J Thromb Haemost 2020;00:1.

Submitted May 25, 2020; accepted Jul 30, 2020.