Brief Communication

Acute Arterial Lower-Limb Ischemia in COVID-19 Patients: Case Series Report

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Abstract

The COVID-19 pandemic has caused more than 2.8 million deaths worldwide to date. Efforts have been made to clearly understand the pathophysiological mechanisms to achieve comprehensive management and achieve a definitive cure. It is known that at the hematological level, there are certain peculiarities that are notable according to the severity within the general context of a prothrombotic state. We present 5 elderly patients with varying severity of acute respiratory distress syndrome due to SARS-CoV-2. During hospitalization, each patient experienced acute arterial ischemia of the lower extremity despite anticoagulation therapy, requiring surgical intervention.

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Key words: acute respiratory distress syndrome, arterial thrombosis, embolism, SARS-CoV-2

SARS-CoV-2 virus has been responsible for a significant number of deaths worldwide, and medical researchers are conducting multiple studies to clearly understand the natural history of this infectious-contagious disease, as well as therapeutics to control it. At this point, there is a lack of effective treatments because there are several peculiarities in the pathophysiology of the virus.

An incidence of thromboembolic events between 5%-15% has been reported in patients with severe respiratory syndrome caused by the SARS-CoV-2 virus, in which a combination of pathophysiological mechanisms of disseminated intravascular coagulation (DIC) with thrombotic microangiopathy-localized disease in the lungs and other organs leads to multiorgan dysfunction.[1] These mechanisms are encompassed in 3 main axes: (1) endothelial lesions due to the affinity of the virus for angiotensin-converting enzyme (ACE) II receptors;[2] (2) blood stasis in immobilized patients, especially those with moderate-to-severe acute respiratory distress syndrome (ARDS); and (3) impact on intensive care and intermediate units.[3] Hypercoagulability due to significant systemic inflammation expresses itself through conditions such as myocardial infarction, cerebrovascular accidents, and acute peripheral arterial ischemia and thrombosis.[4]

The relationship between SARS-CoV-2 and ACE II receptors (lung, blood vessels, heart, kidney, liver, and intestine) promotes apoptosis and activation of endothelial cells, as well as high levels of factor Von Willebrand and factor VIII.[5] This cellular injury activates an enormous amount of proinflammatory cytokines (IL-1, IL-6, TNF), which increase the levels of vascular endothelial growth factor and reduce E-cadherin molecules. In addition, there is an alteration of the binding of tissue factor to factor XI in the extrinsic pathway and expression of several immunoactive molecules, including an increase in the expression of antiphospholipid syndrome antibodies, which leads to a state known as the "cytokine storm" and stimulates the generation of thrombin and deposits of fibrin at the microvascular level, manifesting as microvascular thrombosis in different target organs.[6]

As described, the alteration of hemostasis is widely linked to the pathogenesis of SARS-CoV-2, taking as a starting point the entry of this pathogen into endothelial cells, inducing a significant release of plasminogen activator inhibitor 1 (PAI-1) with the subsequent inhibition of fibrinolysis that is frequently observed in severe stages. A relevant decrease in antithrombin has also been reported due to an increase in vascular permeability within the context of systemic inflammation, which goes hand in hand with the already mentioned expression of tissue factor and with all the pathophysiological circumstances expressed, and places the patient in a significant procoagulant state.[7] Thromboembolic events, such as acute peripheral arterial thrombosis and embolism, are presented in the following clinical cases of acute arterial ischemia of the limb in 5 COVID-19 patients (Tables 1 and 2).

Table 1. Report of the presented COVID-19 clinical cases.

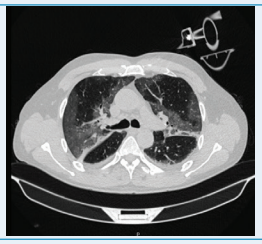
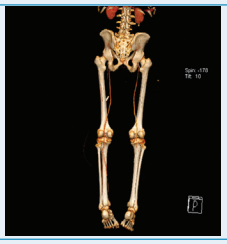
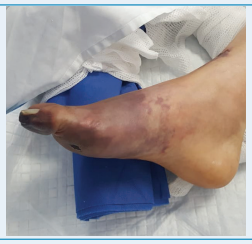
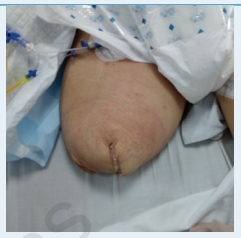
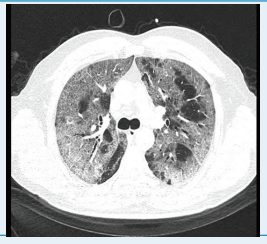
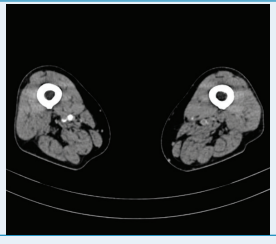
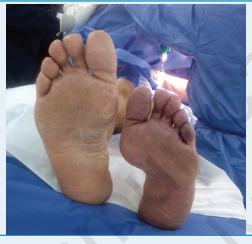
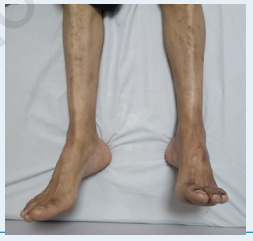
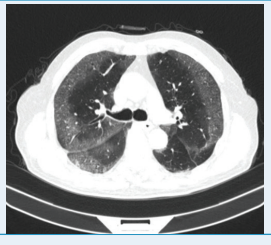
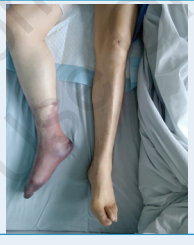
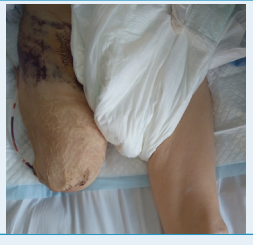
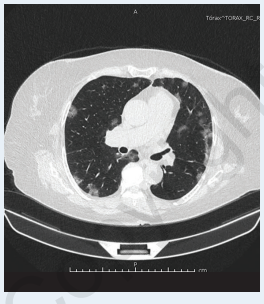
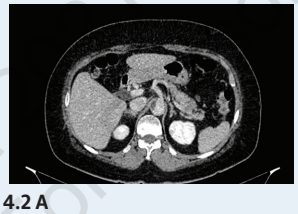
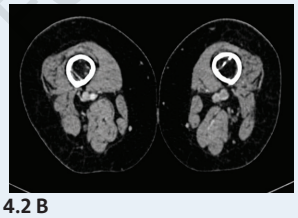
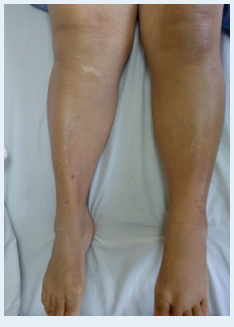
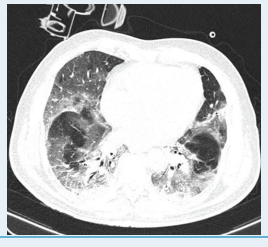
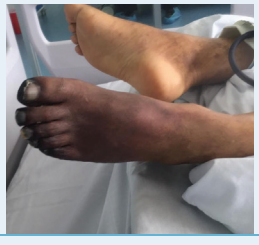
Data	Case 1	Case 2	Case 3	Case 4	Case 5
Age	68 years	66 years	74 years	67 years	73 years
Sex	male	male	male	female	male
Ward of admission	Internal Medicine/ COVID-19; ICU	Internal Medicine/ COVID-19	Internal Medicine/ COVID-19	Internal Medicine/ COVID-19	Internal Medicine/ COVID-19; ICU
Respiratory symptoms	severe dyspnea	severe dyspnea	moderate dyspnea	moderate dyspnea	hoarseness with dyspnea on small effort
History	chronic ischemic heart disease/clopidogrel	none	prostate and testicular surgery 3 months ago due to a neoplasia	type III obesity, controlled arterial hypertension and hypothyroidism	none
Hemodynamic status	stable/NEWS 2: low-medium clinical risk	stable/NEWS 2: high clinical risk	stable/NEWS 2: high clinical risk	stable/NEWS 2: medium clinical risk	unstable/NEWS 2: high clinical risk
Lab examinations					
Complete blood count	leukocytosis with neutrophilia and thrombocytopenia	leukocytosis with neutrophilia	leukocytosis with neutrophilia	leukocytosis with mild neutrophilia	no leukocytosis
Kidney function test	normal parameters	normal parameters	normal parameters	normal parameters	elevated
Liver function test	normal parameters	normal parameters	normal parameters	normal parameters	elevated
Coagulation profile	normal parameters	normal parameters	normal parameters	normal parameters	normal parameters
CT examination	44% pulmonary involvement with CORADS 5 compatibility for COVID-19 (Figure 1.1)	80% lung involvement CORADS 5 compatibility with COVID-19 (Figure 2.1)	68% lung involvement CORADS 5 compatibility with COVID-19 (Figure 3.1)	52% pulmonary involvement with CORADS 5 classification of compatibility with COVID-19 (Figure 4.1)	76% lung involvement, with a CORADS 5 compatibility with COVID-19 (Figure 5.1)
RT-PCR (COVID-19)	positive	positive	positive	positive	positive
Medical treatment	LMWH (enoxaparin) 1 mg/kg twice daily, inotropics, antibiotic (meropenem), cortico-steroids	LMWH (enoxaparin) 1 mg/kg twice daily, clarithromycin + ceftriaxon, corticosteroids	LMWH (enoxaparin) 1 mg/kg twice daily, antibiotic (piperacilina + tazobactam), corticosteroids	LMWH (enoxaparin) 1 mg/kg twice daily, paracetamol	LMWH (enoxaparin) 1 mg/kg twice daily, antibiotic (meropen-em), sedo-analgesia, corticosteroids
Oxygen requirement	4 liters/nasal catheter, deterioration until the need for IMV in ICU	high-flow non-invasive ventilator CPAP system	high flow of O_2 by Ventury system	low-flow O_2 by nasal catheter	high-flow non-invasive ventilator CPAP system, then IMV
Vascular status	On his 18th day of stay, cyanosis, coldness of the toes and right forefoot, absence of popliteal, ATA, PTA, and dorsalis pedis pulses; femoral pulse okay.	Severe pain in the lower left limb of 72-hour duration. Physical examination: pain, digital and the sole of the foot associ-ated with cyanosis, coldness up to distal third of the leg, pro-longed capillary filling, absence of popliteal, ATA, PTA pulses. Conserved mobility at the ankle joint, absent of Doppler signal from the popliteal artery toward distal arteries, presence of venous signal.	Severe pain in right lower limb of 3-day duration, coldness, cyanosis of the foot extending up to the middle third of the leg, loss of movement and sensation, absence of popliteal, ATA, and PTA pulses.	Moderate-to-severe pain with limitation of movement in the left-lower extremity of 7-day duration. On examination, coldness, painful at the foot and leg, with mild digital cyanosis, prolonged capillary filling, absence of popliteal, ATA and PTA pulses, confirmed with eco duplex ultrasound.	On his 5th day of stay, dry gangrane of the left foot, absent of dorsalis pedis, ATA, PTA pulses, popliteal pulse is weak, femoral was not examined because he was in prone position. No signs of infection were observed.

Table 1. Report of the presented COVID-19 clinical cases.

Data	Case 1	Case 2	Case 3	Case 4	Case 5
CT angiography	Absence of contrast at the infrapopliteal arteries. (Figure 1.2)	Total occlusion of left SFA to distal arterial tree with the presence of multiple collaterals. (Figure 2.2)	none	Presence of adherent thrombus occupying 30% of the lumen at the level of the abdominal aorta, thrombotic occlusion of the left common iliac artery and left internal iliac artery, in addition to thrombosis of the left deep femoral artery with total occlusion associated with collateralization phenomen, thrombosis left infrapopliteal segment with several collaterals. (Figure 4.2, A and B)	none
Diagnosis	Acute arterial ischemia of right lower limb (Rutherford class IIB). (Figure 1.3)	Acute ischemia of left lower limb (Rutherford class IIB). (Figure 2.3)	Acute ischemia of right lower limb (Rutherford class IIB). (Figure3.3)	Acute arterial ischemia of the left lower limb due to multisegmental thrombotic occlusion with significant collateralization (Rutherford class I).	Acute arterial ischemia of left lower limb (Rutherford class III). (Figure 5.2)
Surgical intervention	Thrombembolectomy below-knee medial popliteal approach.	Femoral approach thrombembolectomy was performed, abundant subacute thrombi are obtained, with subsequent good back flow, and recovery of distal pulses from the limb, color duplex ultrasound that shows the presence of an arterial distal pulse with biphasic wave.	Urgent surgical intervention is decided, femoral approach thrombembolectomy was performed, subacute thrombi was extracted, trying again thrombectomy, after which obtained poor back flow, absent distal pulses.	Thrombembolectomy of the iliac-femoral popliteal segments was performed within the left femoral approach, obtaining a good proximal and back flow from the SFA with recovering distal pulses.	Plan radical amputation. However, due to the hemodynamic instability of the patient, this procedure was postponed. Finally, the patient died from another causes.
Postoperative period	New thrombosis of dorsalis pedis artery with dorsal arch, dry gangrene.	Postoperatively, patient with palpable peripheral distal pulses, warm limb, capillary filling about 2 seconds. (Figure 2.4)	No improvement and at 48 hours dry necrosis of the digital pulps and heel of the foot is observed, increased cyanosis and pain in the limb. (Figure 3.2)	Transient foot edema, with pain on walking, which was recovered before discharge by rehabilitation physiotherapy. (Figure 4.3)	none
Secondary intervention	Above-knee amputation. (Figure 1.4)	none	Above-knee amputation. (Figure 3.3)	none	none

CBC = complete blood count; CT = computed tomography; RT-PCR = real-time reverse transcription polymerase chain reaction; IMV = invasive mechanical ventilation; ICU = intensive care unit. NEWS 2 = National Early Warning Score 2.
Source: database of the digital hospital health system.

Table 2. Images of the 5 clinical cases presented.

Case	Chest CT	CT Angiography of Lower Limbs	Before Surgery	After Surgery
1	1.1 	1.2 	1.3 	1.4 
Informed consent has been obtained from the family for publication of the case report and accompanying images.				
2	2.1 	2.2 	2.3 	2.4 
Informed consent has been obtained from the family for publication of the case report and accompanying images.				
3	3.1 	NOT AVAILABLE	3.2 	3.3 
Informed consent has been obtained from the family for publication of the case report and accompanying images.				
4	4.1 	4.2 A  4.2 B 	NOT AVAILABLE	3.3 
Informed consent has been obtained from the family for publication of the case report and accompanying images.				
5	5.1 	NOT AVAILABLE	5.2 	NOT AVAILABLE
Informed consent has been obtained from the family for publication of the case report and accompanying images.				

Source: database of the digital hospital health system.

Methods

Five clinical cases were collected from the beginning of the contingency due to the current COVID 19 pandemic in March, 2020 through September, 2020 at the IESS Quito Sur Hospital in Ecuador, which is cataloged as a sentinel hospital for the care of infected patients with COVID-19 (Tables 1 and 2). In order to be included, patients had to present a respiratory condition secondary to the SARS-CoV-2 virus confirmed by polymerase chain reaction, associated with acute limb ischemia after having acquired said infection (severity was defined according to the Rutherford classification for acute ischemia), with prior authorization from the institution. A bioethics letter guaranteed the ethical principles of the study, and clinical records were analyzed. All patients were managed by the authors of this article.

Discussion

The SARS-CoV-2 virus has particular pathophysiological mechanisms that are importantly related to coagulation system alteration, which causes both arterial and venous thromboembolic events that are more noticeable in a seriously ill patient. A study by Klok et al reports an incidence of thrombotic conditions of 31% in the intensive care unit, with 3.7% due to arterial conditions.[1] We report 5 cases in our hospital of acute arterial ischemia of lower limbs due to thrombosis.

All of our patients were older adults, and included 4 men and 1 woman. A similar reality is expressed in an article by Bellosta et al for the European Society for Vascular Surgery that reported a series of 20 patients, in which 90% were male, with an age range between 62 and 95 years.[9] The predominance of hypercoagulability in Virchow's triad is generally exhibited by patients with hemostasis alterations, such as young women; however, our cases correspond to older male patients, thus contributing to the prothrombotic state generated by infection with SARS-CoV-2 virus as the etiology of acute arterial ischemia, despite anticoagulation with low-molecular-weight heparin. Bellosta et al observed that 75% of their patients had acute arterial limb ischemia in stage IIB according to Rutherford classification.[9] Similarly, the 5 patients in the current case series include 1 patient (20%) in Rutherford class I, 3 patients (60%) in Rutherford class IIb, and 1 patient (20%) in Rutherford class III.

Kashi et al reported 7 cases in intensive care patients, of which 5 were classified with irreversible ischemia despite the anticoagulant treatment they received, and emphasize the concern about rapid progression as well as unusual disease sites, such as at the aortic level.[10] This is largely explained by the exaggerated activation of coagulation in the context of systemic inflammation with widely elevated levels of interleukin, such as IL-6, manifesting itself with fibrinogen levels, D-dimer, and sedimentation rate globular cells increased in correlation with the severity of the disease.[6]

The severity of the clinical picture expressed by significant respiratory distress that required management with non-invasive mechanical ventilation at high flows or with invasive mechanical ventilation in our patients highlights the vulnerability to developing thrombosis. As previously mentioned, the activation of the cascade of coagulation, together with the cytokine storm,[2] increases the probability of pulmonary microthrombosis or macrothrombosis with the worsening of patients, and of course the development of peripheral vascular thrombosis.[11]

Diffuse thrombotic microangiopathy as a consequence of aggressive complement activation and its possible relationship with endothelial damage by this virus[12] explain the findings in autopsies where diffuse alveolar damage and inflammation of the airways have been evidenced.[13] Given the intimate association between the severity of the respiratory condition and the increased probability of presenting with thromboembolic events, it was therefore determined that 4 of our 5 reported patients presented with severe respiratory insufficiency (PO_2/FiO_2 ratio <200), and 2 of the patients died due to multiple organ failure. Furthermore, there is a lack of evidence to determine whether or not the endothelial damage produced by COVID-19 would result in successful revascularization, as 2 of the patients required major amputation due to an unfavorable outcome after thrombembolectomy.

It is important, therefore, to highlight the high probability of developing thromboembolic events in positive COVID-19 patients despite anticoagulation and become familiar with their clinical manifestations, which can identify patients who are candidates for revascularization, such as palpation of distal pulses in patients with severe acute respiratory syndrome, and maintaining the recommendations on therapeutic anticoagulation, with an emphasis on the control of risk factors clearly related to a worse prognosis of the disease, such as arterial hypertension, diabetes, cardiovascular disease, and obesity.[14]

Conclusion

We present a series of 5 positive COVID-19 patients who developed acute arterial lower-limb ischemia that required surgical management. All of the patients were older adults, and most had severe acute respiratory syndrome. These cases emphasize the importance of vascular semiology in COVID-19 patients due to the likelihood of thromboembolic events despite anticoagulation.

References

1. Levi M, Thachil J, Levy JH, et al. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol*. 2020;7:e438.

2. Fan BE, Chia YW, Sum CLL, et al. Global haemostatic tests in rapid diagnosis and management of COVID-19 associated coagulopathy in acute limb ischaemia. *J Thromb Thrombolysis*. 2020;50:292-297.

3. Mestres G, Puigmacià R, Blanco C, et al. Risk of peripheral arterial thrombosis in COVID-19. *J Vasc Surg*. 2020;72:756-757.

4. Violi F, Pastori D, Cangemi R, et al. Hypercoagulation and antithrombotic treatment in coronavirus 2019: a new challenge. *Thromb Haemost* 2020;120:949-956.

5. Langer F, Kluge S, Klamroth R, et al. Coagulopathy in COVID-19 and its implication for safe and efficacious thromboprophylaxis. *Hamostaseologie*. 2020;40:264-269.

6. Kasinathan G, Sathar J. Haematological manifestations, mechanisms of thrombosis and anti- coagulation in COVID-19 disease: a review. *Ann Med Surg* 2020;56:173-177.

7. Iba T, Levy JH, Connors JM, et al. The unique characteristics of COVID-19 coagulopathy. *Crit Care*. 2020;24:360.

8. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res.* 2020;191:145-147.

9. Bellosta R, Luzzani L, Natalini G, et al. Acute limb ischemia in patients with COVID-19 pneumonia. *J Vasc Surg*. 2020;72:1864-1872.

10. Kashi M, Jacquin A, Dakhil B, et al. Severe arterial thrombosis associated with COVID-19 infection. *Thromb Res*. 2020;192:75-77.

11. Hamilton KV, Hussey KK. Intra-arterial thrombosis associated with COVID-19. *J Vasc Surg*. 2020;72:757-758.

12. Kaur P, Qaqa F, Ramahi A, et al. Acute upper limb ischemia in a patient with COVID-19. *Hematol Oncol Stem Cell Ther*. Epub 2020 May 13.

13. Barton LM, Duval EJ, Stroberg E, Ghosh S, Mukhopadhyay S. COVID-19 autopsies, Oklahoma, USA. *Am J Clin Path*. 2020;153:725-733.

14. Jordan RE, Adab P, Cheng KK. COVID-19: risk factors for severe disease and death. *J Vasc Surg.* 2020;72:757-758. Epub 2020 May 17.

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Disclosure: The authors have completed and returned the ICMJE Form for Disclosure of Potential Conflicts of Interest. The authors report no conflicts of interest regarding the content herein.

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The authors report that patient and/or family consent was provided for publication of the images used herein.

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