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Case Report

Acute limb ischemia in patient with COVID-19 infection

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2, the virus that causes coronavirus disease 2019 caused a worldwide pandemic and became a massive problem in our healthcare system. This infection has broad clinical presentation from asymptomatic to severe symptoms, and unfortunately death. Hypercoagulability associated with this infection can cause a significant morbidity, that increased risk of microthrombosis, vascular hyperpermeability, disseminated intravascular coagulation, and multiorgan failure. Acute limb ischemia (ALI) is the one of coronavirus disease 2019 associated coagulopathy that threaten the limb viability in a very short interval. We report a case of a 98-year-old woman with coronavirus disease 2019 infection, then suddenly has ALI in the right foot.

Keywords: Acute limb ischemia, COVID-19, Hypercoagulability, SARS-CoV-2

INTRODUCTION

Coronavirus disease 2019 (COVID-19) infection is one of the wide-spread infectious diseases that has been a massive problem in the world and has become a global disaster for our society. COVID-19 infection has a broad clinical spectrum from asymptomatic to severe symptoms, and unfortunately death.[1] COVID-19 clinical manifestations, including bilateral pneumonia, acute respiratory distress syndrome (ARDS), endothelial dysfunction, hypercoagulability, and multiorgan failure. Elevated procoagulant factors coupled with the overproduction of cytokines lead to an increased risk of microthrombosis, vascular hyperpermeability, disseminated intravascular coagulation (DIC), and multiorgan failure. COVID-19 associated coagulopathy (CAC) includes both arterial and venous thromboembolism (VTE). Arterial thrombosis in COVID-19 patients can shows in different forms, from blue-toe syndrome to limb-threatening ALI.[2-4]

ALI is defined by sudden decrease in arterial perfusion that threatens limb viability in which occurs within 14 days after symptom onset. ALI threatens limb viability in a very short interval, because there is insufficient time for new blood vessel growth to compensate for the loss of perfusion. The sudden ischemia affects skin, muscles and nerves of the limbs which leads to the necrotic and tissue death. The severity of ALI is graded according to the Rutherford classification (Table 1) that plays a major role in decision making and assessment of significant comorbidities.[5] Urgent revascularization is required to preserve limb viability.[5,6]

The incidence of ALI is approximately 1.5 cases per 10,000 people per year.[5,7] During COVID-19 pandemic, ALI occurred approximately five times more frequently in COVID-positive patients. COVID-19 can precipitate arterial thrombotic events through mechanisms including endothelial injury.[7] Here we present a case of ALI in a patient with COVID-19 infection.

Table 1: Stages of ALI according to the Rutherford classification.[5]

Class	Prognosis	Findings		Doppler Signal	
		Sensory loss	Muscle weakness	Arterial	Venous
I	Limb viable, not immediately threatened	None	None	Audible	Audible
IIa	Limb marginally threatened, salvageable if promptly treated	Minimal (toes)	None	Often inaudible	Audible
IIb	Limb immediately threatened, salvageable with immediate revascularization	More than toes, pain at rest	Mild or moderate	Inaudible	Audible
III	Limb irreversibly damaged, major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Paralysis (rigor)	Inaudible	Inaudible

CASE REPORT

A 98-year-old woman complained about a general weakness, nausea and loss of appetite which started to develop 1 week before admission. In the last 3 days before admission, the patient refused to eat and only took a little water. Patient also complained about coughing and fever before admission.

At admission, the patient's consciousness was somnolent with blood pressure was 80/40 mmHg after loading 1 flash of normal saline, heart rate was 130x/minute, respiratory rate was 24x/minute, temperature was 36.4^{O}C, and oxygen saturation was 97% with 2 liters oxygen via nasal cannula. On a physical examination, rhonchi was found on both lungs. On initial laboratory examination, the following values were noted: hemoglobin 8.9 g/dL (11.7-15.5 g/dL), total leucocyte count 9.34×10^3/uL (3.60-11.00×10^3/uL), absolute neutrophil count 15.4×10^3/uL (1.50-7.00×10^3/uL), absolute lymphocyte count 1.44 x 10^3/uL (1.00-3.70×10^3/uL), platelet 258 10^3/uL (150-440 10^3/uL), blood urea nitrogen 59 mg/dL (6-20 mg/dL), serum creatinine 1.97 mg/dL (0.51-0.95 mg/dL), serum natrium 149 mmol/L (136-145 mmol/L), serum kalium 5.4 mmol/L (3.5-5.1 mmol/L), prothrombin time 20.8s (7.9-10.3 s), international normalized ratio 1.85, activated partial thromboplastin time 79.7s (20.0-30.3s). Blood gas analysis significant for mixed metabolic acidosis and respiratory alkalosis. Chest x-ray showed multifocal infiltrates and honeycomb appearance with suggest for pneumonia and bronchiectasis. Nasopharyngeal swab was positive for SARS-CoV-2 with Ct value 28.75. Electrocardiography showed sinus tachycardia of 114 beats/minute. Patient started initial therapy with azithromycin, ceftriaxone, favipiravir and n-acetylcysteine.

On day 3 of hospitalization, the patient reported suddenly blackish blue at the right foot with minimal pain at rest and weak pulse on palpation at dorsalis pedis artery. Patient can still move her right foot slightly. A Doppler ultrasound showed hypoechoic lesion (intraluminal thrombus) on right popliteal artery, right posterior tibial artery, right common and superficial femoral vein, right popliteal vein, and right posterior tibial vein, prominent calcification that caused 47% stenosis on arterial lumen on the right distal superior femoral junction, intermittent calcification on right common femoral artery, right superficial femoral artery, right anterior tibial artery, and right dorsalis pedis artery, calcification plaque on the right popliteal artery that caused about 75% luminal stenosis, and no vascularization was seen on right posterior tibial artery and right dorsalis pedis artery. The patient was diagnosed with ALI right inferior extremity Rutherford class IIb et causa thrombus in region ⅓ medial and ⅓ right distal femoral. The patient was started on anticoagulant therapy with unfractionated heparin and referred to other hospital to perform a thrombectomy.

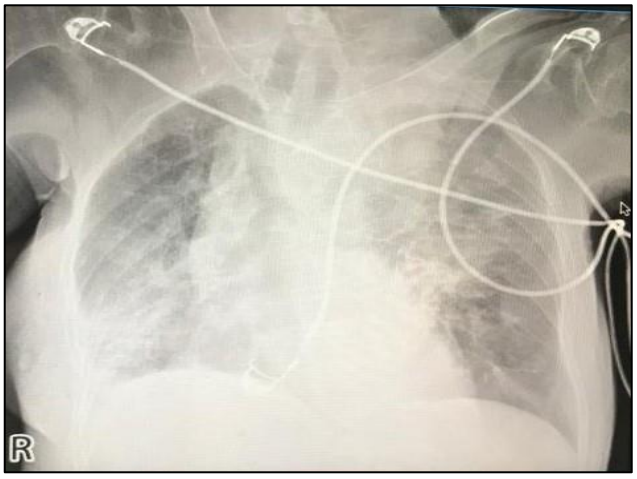

Figure 1: Chest x-ray of the patient.

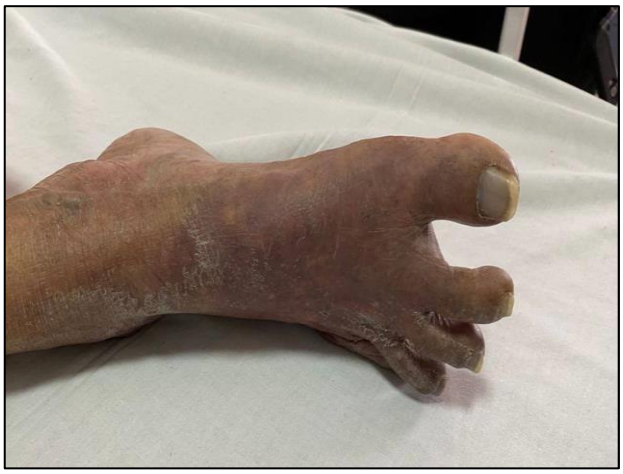

Figure 2: Blackish blue discoloration on right foot.

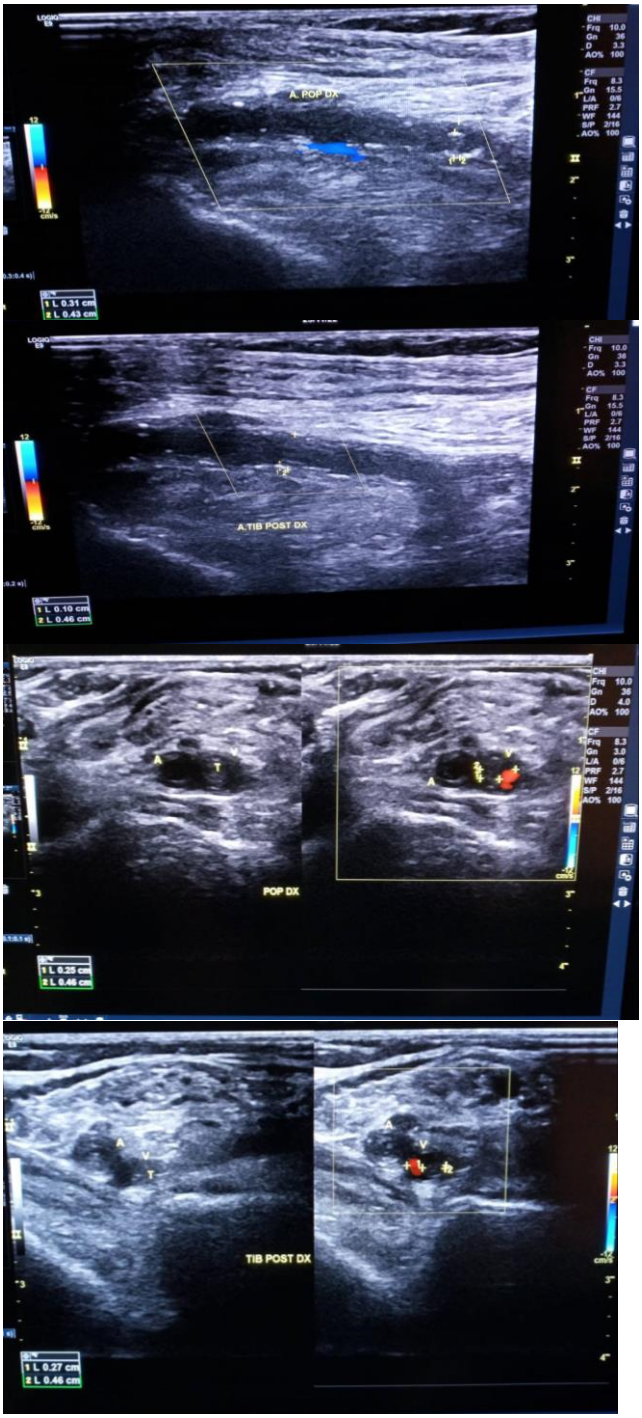

Figure 3: Doppler ultrasound.

DISCUSSION

In this study, we reported a case of a patient with ALI on COVID-19 infection. The symptom of COVID-19 is continuing to evolve. The most common symptoms are fever, myalgia, cough, and dyspnea, and less frequently headache diarrhea, nausea, and vomiting. Severity of infection could be varied from asymptomatic infection to critical disease. Although in COVID-19 respiratory symptoms are predominant, thrombosis can occur with COVID-19. Among patients with advanced age and medical comorbidities, COVID-19 is frequently severe. Patients with COVID-19 infection can develop a disseminated coagulopathy by increased procoagulant factors leading to widespread vascular thrombosis.[3]

ALI is defined as an abrupt decrease in arterial perfusion of a limb with a threat to viability of the limb. The clinical presentation is considered to be acute if symptom duration is less than 2 weeks.[5,8,9] The classical clinical features of patients with ALI are pain, pallor, paralysis, pulse deficit, paresthesia, and poikilothermia. Symptoms develop in several minutes, to hours or days, and range from new or worsening intermittent claudication to severe rest pain, paresthesia, muscle weakness, paralysis and even gangrene.[5,10] In this patient, we found the symptoms of ALI, in which: pallor, paralysis, pulse deficit, and the symptom develop in acute duration. From the symptoms that according to the Rutherford classification, we diagnosed this patient with Rutherford stage IIb.

The mechanism of ALI in patients with COVID-19 infection is complex, involving not only the coagulation system, but also immune system, endothelium, and platelets. A combination of the direct viral infection of endothelial cells by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and endothelial cell response to the inflammatory process associated with COVID-19 that upregulates immune cell responses, production of cytokines, and activation of complement probably mediates endothelial damage and microvascular thrombosis. COVID-19 infection can cause thrombotic phenomena starting with viral invasion of endothelial cells via angiotensin-converting enzyme 2 (ACE2) receptors. In the endothelium, SARS-CoV-2 can infect the pericytes and perivascular cells present on the surface of microvessels. Pericytes play an important role in vascular homeostasis and regulation of the inflammatory process. Therefore, abnormalities of pericytes may cause tissue injury that can lead to organ damage. Abundant expression of ACE2 receptors on endothelial cells enhances their vulnerability to SARS-CoV-2 binding, membrane fusion, and viral entry, causing infection and resultant vascular injury and dysfunction.[2,11,12]

Patients with COVID-19 are present in a hypercoagulation state that is triggered by deep and complex inflammatory response to the virus and this procoagulant state contributes to arterial thrombosis.[2,8,12] Hypoxia contributes to coagulopathy by converting the normal phenotype of the endothelium (resistant to thrombotic activity) to a prothrombotic phenotype through the increased transcription of the early growth response gene 1 and hypoxia-inducible factor 1.[2,13] Increased level of proinflammatory cytokines (IL-1, IL-2, IL-6, IL-7, G-CSF, TNF, IP-10, MCP1, MIP1-α, etc) in the patients which leads to cytokine release syndrome (CRS).[2,5,14] COVID-19 infections cause increased levels of helper T lymphocytes, which excessively produce CD14 and CD16. COVID-19 also stimulates excessive production of IL-1, then initiates cytokine cascade and enhances the

production of IL-6, which is a key mediator in COVID-19. IL-6 is a cytokine that triggers inflammatory cells to invade the tissue and induce endothelial injury and production of acute-phase reactants (APRs), including CRP and fibrinogen from the liver. These two APRs play an important role in inducing the hypercoagulable state in the body and thus leading to thrombosis. Endothelial injury leads to exposure of von Willebrand factor, which leads to further thrombotic activity.[2,7,15] In COVID-19 patients, there is also an alteration of the fibrinolytic system secondary to the increase in angiotensin II and secondarily to type 1 plasminogen activator inhibitor (PAI-1) which by blocking the plasminogen activators (t-PA and u-PA) induces a state of hypofibrinolysis and thrombosis.[13,16]

The therapeutic strategy will depend on the presence of a neurological deficit, location, Rutherford class, duration of ischemia, comorbidities, and therapy-related risks and outcomes.[9] Patients with clinical suspicion of ALI should be addressed to the emergency centers for immediate diagnosis and management. Urgent anticoagulation with unfractionated heparin (UFH) prevents thrombus propagation and preserves microcirculation.[5,16] Heparin has suppressive activity against the development of cytokine storms. Also, heparin has competitive binding activity to the coronavirus that results in a significant reduction of the pathogen activity by inhibiting cell penetration.[16] Revascularization is needed depending on Rutherford classification. Class I ALI is treated with anticoagulation alone. If revascularization is necessary, both endovascular and open surgical intervention are available. Class II ALI, where the limb is salvageable with prompt intervention, either endovascular or open surgical technique or hybrid approach can be chosen. Additional open techniques might be warranted especially in the class IIb setting. In patients with class III ALI, revascularization is not indicated and amputation should be considered.[5,9,17] In patients with critically threatened limbs, local venous acidosis should be assessed to predict adverse outcomes and reperfusion injury. If present, acid-base and electrolyte imbalance should be corrected as soon as possible. A careful observation of kidney function before and after revascularization is recommended, especially in older patients or in patients with prior kidney disease.[5]

CONCLUSION

COVID-19 infection has become a global problem for our society. This infection is even associated with an increased incidence of thromboembolic events, including ALI. ALI is a vascular emergency that is serious and threatens the limb viability in a very short interval. Rapid diagnosis and management is needed in order to preserve the limb viability.

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REFERENCES

1. Surya SP, Santoso RM. A clinical case series of COVID-19-associated acute limb ischemia: real-world situation. Egypt Heart J. 2021;73(59):1-7.
2. Hasan SA, Haque A, Nazir F. Acute Limb Ischemia: A Rare Complication of COVID-19. Cureus. 2020;12(11):1-6.
3. Singh B, Kaur P, Aldir N, Gupta S, Maroules M. COVID-19 Presenting as Acute Limb Ischemia. Cureus. 2020;12(7):1-4.
4. Barac S, Onofrei RR, Neagoe PV, Popescu AI. An Observational Study on Patients with Acute Limb Ischemia and SARS-CoV-2 Infection: Early and Late Results in Limb Salvage Rate. J Clin Med. 2021;10(5083):1-10.
5. Olinic DM, Stanek A, Tataru DA, Homorodean C, Olinic M. Acute Limb Ischemia: An Update on Diagnosis and Management. J Clin Med. 2019;8(1215):1-12.
6. Topcu AC, Altunyurt GO, Akman D, Batirel A, Demirhan R. Acute Limb Ischemia in Hospitalized COVID-19 Patients. Ann Vasc Surg. 2021;74:88-94.
7. Ilonzo N, Judelson D, Al-Jundi W, Yana E, et al. A review of acute limb ischemia in COVID-positive patients. Seminars in Vascular Surg. 2021;24:8-12.
8. Topcu AC, Ariturk C, Yilmaz E. Acute limb ischemia in a COVID-19 patient. Thrombosis Update. 2021;100044:1-4.
9. Aboyans V, Ricco JB, Bartelink ML, Bjorck M, Brodmann M. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Eur Heart J. 2018;39(9):798-99.
10. Hage AN, McDevitt JL, Chick JF, Vadlamudi V. Acute Limb Ischemia Therapies: When and How to Treat Endovascularly. Sem Interven Rad. 2018;35:453-60.
11. Gu SX, Tyagi T, Jain K, Gu VW, Lee SH et al. Thrombocytopathy and endotheliopathy: crucial contributors to COVID-19 thromboinflammation. Nature Rev Cardiology. 2021;18:194-209.
12. Ortega-Paz L, Capodanno D, Montalescot G, Angiolillo DJ. Coronavirus Disease 2019-Associated Thrombosis and Coagulopathy: Review of The Pathophysiological Characteristics and Implications for Antithrombotic Management. J Am Heart Assoc. 2021;10:1-24.
13. Lorini FL, Matteo MD, Gritti P, Grazioli L. Coagulopathy and COVID-19. Eur Heart J. 2021;23(E):95-8.
14. Al-zoubi N, Shatnawi N, Jarbo H. Acute Lower Limb Ischemia in Patients Infected with COVID-19. Int J General Surg. 2021;14:833-39.
15. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood. 2020;135(23):2033-40.

16. Bellosta R, Luzzani L, Natalini G, Pegorer MA. Acute limb ischemia in patients with COVID-19 pneumonia. J Vasc Surg. 2020;72(6):1864-72.
17. McNally MM, Univers J. Acute Limb Ischemia. Surg Clin N Am. 2018;98:1081-96.

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