

Peripheral ischemic limb necrosis (Acro-ischemia) associated with severe COVID-19 patients (COVID-19 limbs): A report of three cases

Khaled Khattab¹, Axel Tobias Kempa¹, Riza Atas¹, Harun Asani¹, Ahmed Ehab^{1,2}

¹Department of Pulmonary and Critical Care Medicine, Lowenstein Lung Center, Lowenstein, Germany, ²Department of Pulmonary Medicine, Mansoura University, Egypt

ABSTRACT

The association between severe coronavirus disease 2019 and hypercoagulable state was observed in many reports. This may be explained by the presence of hypoxia, severe systemic inflammatory response, immobilization due to intensive care unit (ICU) admission, and diffuse intravascular coagulation. We report three patients who were admitted to our respiratory ICU with acute severe respiratory distress syndrome (ARDS) requiring mechanical ventilation due severe acute respiratory syndrome coronavirus 2 infection, who developed severe limb ischemia during the course of the disease.

KEY WORDS: ARDS, coronavirus disease 2019, D-dimer, limb ischemia, severe acute respiratory syndrome coronavirus 2

Address for correspondence: Dr. Ahmed Ehab, Department of Pulmonary and Critical Care Medicine, Lowenstein Lung Center, Lowenstein, Germany.
E-mail: dr.a.ehab@gmail.com

Submitted: 09-Jun-2020

Accepted: 14-Jun-2020

Published: 06-Mar-2021

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel enveloped RNA beta-coronavirus which, since December 2019, has spread in China and the rest of the world and was later declared a pandemic from the World Health Organization (WHO). At the time of writing of this report, over than 6 million cases worldwide with about 370,000 deaths were reported.^[1]

A coincidence of thromboembolic vascular events in patients with severe coronavirus disease 2019 (COVID-19) has been reported in many patients with increased D-dimer levels.^[2] Some cases of disseminated intravascular coagulopathy (DIC) by homeostasis alterations were also described.^[3,4] Sepsis and severe hypoxemia contribute also to the pathogenesis.

In this report, we describe three cases of patients with acute severe respiratory distress syndrome (ARDS) caused by SARS-CoV-2 infection, who developed limb necrosis during the course of the disease.

CASE REPORTS

Case 1

We report the case of a 75-year-old female patient with a history of atrial fibrillation under oral anticoagulation therapy and hypertension, who has recently underwent prosthetic knee replacement. During the inpatient rehabilitation therapy, the patient was infected by SARS-CoV-2 and developed COVID-19. She deteriorated rapidly to severe ARDS with Horowitz index 85

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Khattab K, Kempa AT, Atas R, Asani H, Ehab A. Peripheral ischemic limb necrosis (Acro-ischemia) associated with severe COVID-19 patients (COVID-19 limbs): A report of three cases. Lung India 2021;38:S58-60.

Access this article online	
Quick Response Code: 	Website: www.lungindia.com
	DOI: 10.4103/lungindia.lungindia_470_20

necessitating mechanical ventilation. At the time of the admission, we observed the presence of ischemic changes in the four extremities which were more severe in the fingers [Figure 1]. Despite the full anticoagulation therapy using IV heparin infusion with PTT in target, the sequential D-dimer values had dramatically increased which eventually correlated to the deterioration in the general condition of the patients. Due to hemodynamic instability, despite the use of catecholamine, the median noradrenaline perfusion rate had not exceeded 0.3 mg/h. The ischemic changes in the limbs were observed before the initiation of noradrenaline therapy. Ultrasound Doppler showed patent flow in both dorsalis pedis arteries and posterior tibial arteries in the foot and patent flow in the median and radial arteries in the left hand, and the flow in the right radial artery was reduced. Based on the sonographic findings, the microthrombosis or small-vessel vasculitis are most probably the cause of the disease. Unfortunately, the patients died due respiratory and multiorgan failure.

Case 2

We report the case of a 76-year-old female with a history of Type 2 diabetes mellitus, arterial hypertension. The patient was mechanically ventilated due severe ARDS (Horowitz-index 86) due SARS-COVID-19 infection and bacterial superinfection. The coagulation profile showed the international normalized ratio (INR) of 1.3. PTT at 41 s, fibrinogen in normal range, platelets slightly decreased (152×10^3), and significant elevation of D-dimer values >35 mg/l (normal test range 0–0.55 mg/l) were noted for the patient. During the admission, ischemic changes were observed in the left big toe [Figure 2]. Based on the clinical course and laboratory changes, the prophylactic anticoagulation was switched into IV heparin perfusion. The ultrasound Doppler confirmed a patent flow in both dorsalis pedis arteries and posterior tibial arteries without obvious thrombotic changes making a possible diagnosis of either microthrombosis or small-vessel vasculitis. After computed tomography (CT) of the thorax evidence of bilateral peripheral pulmonary embolism (PE) was detected. After 20 days of mechanical ventilation, she was successfully extubated, and finally, the patient was discharged with supplemental oxygen.

Case 3

We report the case of a 73-year-old female with a history of recurrent mediastinal non-Hodgkin lymphoma. After the induction of the first cycle of chemotherapy, the patient was diagnosed with severe ARDS due to SARS-COVID-19 infection (Horowitz-index ratio 81). The patient was mechanically ventilated, and prone position was also frequently used. The coagulation profile (INR, activated partial thromboplastin time, and fibrinogen) was in the normal range, however D-dimer was sequentially elevated. Meanwhile, the patient was under mild noradrenaline therapy (median range was at 0.2 mg/h). Ischemic changes in the left toes with necrotic changes in the middle toe without sonographic evidence of blood flow disturbance in the supplying arteries were observed [Figure 3]. Therefore,



Figure 1: Female patient with severe acute respiratory syndrome coronavirus disease 2019 ARDS. Ischemic changes were observed in both the lower and upper limbs with necrosis in the fingers



Figure 2: Female patient with severe acute respiratory syndrome coronavirus disease 2019 ARDS. Ischemic changes in the left toe



Figure 3: Female patient with severe SARS COVID-19 ARDS. Ischemic changes with necrosis in the middle toe

a full anticoagulation therapy using IV heparin perfusion was conducted. Later on, CT chest was done and revealed the presence of peripheral PE. Unfortunately, the condition was complicated with invasive aspergillosis, and the patient died.

DISCUSSION

According to the WHO, the pattern of the COVID-19 infection was classified into: mild (80%), severe (14%), and critical illness including severe ARDS, sepsis, and septic shock in about 5% of the patients.^[5] The vascular and hemostatic dysfunctions among the patients with COVID-19 infection were described in many reports.^[6] Clinically, it represents with the development of PE, myocardial injury, cutaneous manifestations due to thrombotic microangiopathy, and multiorgan failure by large-vessel thrombosis or intravascular coagulation.^[7] Furthermore, autopsies confirmed the formation of fibrin thrombi has been observed and described.^[8]

These vascular changes could be explained by the utilization of ACE2 receptors by the virus. The ACE2

receptor is also widely expressed on pneumocytes as well as endothelial cells that traverse the multiple organs.^[9] The binding between the virus and the ACE2 receptors leads to systemic inflammation as well as endotheliitis that subsequently systemic impaired microcirculatory function in different vascular beds and their clinical sequelae in patients with COVID-19.^[10]

In this case report, we described three cases with ischemic changes that associated with severe COVID-19 infection. The condition could be fully explained with circulatory instability as the minimal dose of the noradrenaline was required. The peripheral arterial disease due to narrowing of the supplying arteries could also be excluded using Doppler sonography. Mostly, the condition could be explained by the presence of microthrombosis or vasculitis that complicates the COVID-19 infection. The possible endotheliitis that associates COVID-19 infection leads to the development of endothelial dysfunction with microvascular dysfunction and vasoconstriction with subsequent end-organ ischemia and subsequent failure.^[11]

In our patients, we observed that vascular changes were associated with increasing level of D-dimer, ferritin, and low albumin. The condition is not associated with changes in fibrinogen or thrombocytopenia. Therefore, DIC was not a possible cause. The elevated D-dimer, ferritin, and low albumin were also used as a marker of severity COVID-19 infection.^[2,12]

All of our patients were under the anticoagulation therapy; nevertheless, the ischemic changes were developed. Whether, the ASS could be used as a prophylaxis still questionable.^[13]

Finally, we described severe ischemic changes in three patients with SARS-COVID 19 ARDS. Two of our patients died due to multiorgan failure. The presence of such ischemic changes is associated with high mortality. The anticoagulation treatment should be used with the rising D-dimer level, however its benefit in the presence of suspected microthrombosis or vasculitis is still not fully effective.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have

given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. WHO Director-General's Remarks at the Media Briefing on 2019-nCoV on 11 February 2020. Available from: <https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020>. [Last accessed on 2020 May 04].
2. Griffin DO, Jensen A, Khan M, Chin J, Chin K, Saad J, *et al.* Pulmonary Embolism and Increased Levels of d-Dimer in Patients with Coronavirus Disease. *Emerging infectious diseases* 2020;26(8).
3. 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.
4. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, *et al.* Hematologic parameters in patients with COVID-19 infection. *Am J Hematol* 2020;95:E131-4.
5. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi* 2020;41:145-51.
6. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, *et al.* Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med* 2020. pii: NEJMoa2015432.
7. Liu PP, Blet A, Smyth D, Li H. The science underlying COVID-19: Implications for the cardiovascular system. *Circulation* 2020; [doi: 10.1161/circulationaha.120.047549].
8. Tian S, Hu W, Niu L, Liu H, Xu H, Xiao SY. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. *J Thorac Oncol* 2020;15:700-4.
9. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020;579:270-3.
10. Long B, Brady WJ, Koyfman A, Gottlieb M. Cardiovascular complications in COVID-19. *Am J Emerg Med* 2020. pii: S0735-6757 (20) 30277-1.
11. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, *et al.* Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020;395:1417-8.
12. Zhang Y, Cao W, Xiao M, Li YJ, Yang Y, Zhao J, *et al.* Clinical and coagulation characteristics in 7 patients with critical COVID-2019 pneumonia and acro-ischemia. *Zhonghua Xue Ye Xue Za Zhi* 2020; 41:302-7.
13. Protective Effect of Aspirin on COVID-19 Patients-Full Text View. Available from: <https://clinicaltrials.gov/ct2/show/NCT04365309>. [Last accessed on 2020 May 31].