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

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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

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.
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 × 10³), 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, 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.[9] 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. 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. 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.

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.

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.

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.

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**Conflicts of interest**
There are no conflicts of interest.

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