Extensive Acute Lower Extremity Arterial Thrombosis: A Major Thrombus Formation Caused by COVID-19

Pouya Tayebi¹, Mahmoud Sadeghi Haddad Zavareh², Gooya Tayyebi³, Fatemeh Zahra Abdollahi⁴, and Fatemeh Mahmoudlou⁴

¹Department of Vascular and Endovascular Surgery, Rouhani Hospital, ²Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, ³Department of Geriatric Psychiatry, Rasoul Akram Hospital, Iran University of Medical Sciences, Tehran, ⁴Student Research Committee, Babol University of Medical Sciences, Babol, Iran

Acute thromboembolic events have been frequently reported in patients with coronavirus disease 2019 (COVID-19) due to an increase in the coagulation system activity and endothelial dysfunction. This report describes a patient with COVID-19 who initially reported respiratory symptoms and developed acute lower limb ischemia secondary to extensive macrovascular arterial thrombosis, which was treated with thrombectomy. The development of such extensive arterial thrombosis with anticoagulants at therapeutic doses is a new sign of increased viral pathogenicity, and it is necessary to develop and apply updated prophylaxis protocols for thrombosis in these patients.

Key Words: Acute limb ischemia, Arterial thrombosis, COVID-19

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Corresponding author: Mahmoud Sadeghi Haddad Zavareh

Infectious Diseases and Tropical Medicine Research Center, Babol University of Medical Sciences, Keshavarz Boulevard, Babol 4717641367, Iran
Tel: 989381915009
Fax: 981132238300
drm_sadeghih@yaho.com
<https://orcid.org/0000-0001-8701-7267>

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INTRODUCTION

After the outbreak of coronavirus disease 2019 (COVID-19) worldwide, various clinical manifestations have been reported in infected patients. In addition to the common respiratory manifestations of the disease, thromboembolic events have also been described [1]. Studies have shown that COVID-19 can increase the levels and activities of pro- and anti-inflammatory cytokines [2,3]. There is also evidence of increased complement activity in these patients, secondary to the viral infection of vascular endothelial cells and increased secretion of anaphylatoxin C5a [4]. Such biological changes in the patient's body, which lead to increased blood coagulation, have already been confirmed by the presence of microclots in the lung microvessels during

the lung autopsies of COVID-19 patients [5]. However, the microclots can turn into larger thrombi, which can lead to thromboembolic events, such as stroke, deep vein thrombosis, pulmonary embolism, and arterial ischemia [6]. The severity of thrombosis in the main arteries of the limbs is usually short [7], but in our patient, a very large thrombosis occurred in the arteries of the lower limbs, which was unique in its kind.

Informed consent was obtained from the patient's family for publication, and this was approved by the ethics committee with reference (no. IR.MUBABOL.REC.1400.100).

CASE

An 80-year-old male patient with a history of diabetes mellitus presented to the emergency department complaining of shortness of breath and cough. His vital signs on presentation were as follows: temperature, 37°C; heart rate, 112 beats/min; blood pressure, 120/75 mmHg; respiratory rate, 28 breaths/min; and oxygen saturation, 90% on supplemental oxygen. There were no significant points in the general examination. His bilateral lower extremities were normal, and his bilateral popliteal, posterior tibial, and dorsalis pedis arterial pulses were palpable. On laboratory testing, the following values were noted: white blood cells, $7 \times 10^9/\text{L}$ (reference, 4.5×10^9 – 11.5×10^9); hemoglobin, 13.6 g/dL (12–16); hematocrit, 37.3% (35%–45%); platelets, $210 \times 10^9/\text{L}$ (140×10^9 – 440×10^9); glucose, 378 mg/dL (70–105); creatinine, 1.4 mg/dL (0.6–1.40); blood urea nitrogen, 11.3 mg/dL (7–23); D-dimer, 248 ng/mL (<0.5); prothrombin time, 20 sec (12.2–14.9); international normalized ratio, 1.1 (<1); partial thromboplastin time, 40 sec (21.3–35.1); C-reactive protein, 151 mg/L (<10 mg/L); and erythrocyte sedimentation rate, 88 mm/h (0–32); lupus anticoagulant, negative; interleukine-6, 76 pg/mL (5–15). His nasopharyngeal swab was positive for the severe acute respiratory syndrome coronavirus-2, and high-resolution computed tomography showed bilateral extensive interstitial lung infiltrates. As such, the patient was admitted to the intensive care unit (ICU) and was treated with Ziferon (Interferon-1b, 250 mg/mL; Zist Daru Danesh, Tehran, Iran) every two days via subcutaneous administration, dexamethasone 8 mg/day

via intravenous administration, Remdesivir (100 mg/20 mL; Actoverco, Tehran, Iran) 200 mg on the first day followed by 100 mg/day, and heparin 5,000 units subcutaneously every 6 hours. On the ninth day after admission, with the patient still complaining of shortness of breath (O_2 saturation: 89%), he experienced sudden pain in the right lower extremity with coldness, ischemic discoloration, paralysis, and lack of femoral pulses of the limb (Fig. 1). Computed tomography angiography revealed the total occlusion of the right common iliac artery with no distal run-off (Fig. 2). Electrocardiography did not show any arrhythmia, and the platelet count was normal on the day of the event and after. The patient underwent an emergency thromboembolectomy with spinal anesthesia via a femoral incision. A long thrombus with a cohesive, tubular consistency emerged from the iliac, femoral, and tibial arteries (Fig. 3, Supplementary Video 1). After the successful thrombectomy, the ischemia resolved, and the patient was transferred to the ICU. In the ICU, the patient experienced respiratory acidosis (pH, 7.27; PCO_2 , 55; PO_2 , 90; HCO_3 , 14.4; base excess, –2.1) but had adequate urine flow. He also received intravenous heparin at a dose of 1,000 units per hour. The right lower extremity was warm, and the symptoms of ischemia resolved. In addition, necessary measures were taken to prevent reperfusion syndrome. Ten hours after the operation, the patient's respiratory distress worsened despite receiving 100% oxygen. He eventually suffered from cardiopulmonary arrest and died.

Fig. 1. The figure showed the discoloration of the right lower limb due to acute limb ischemia in a severely ill COVID-19 patient.

Fig. 2. The reconstructed computed tomography angiography revealed a complete arterial thrombosis in the right lower extremity.

Fig. 3. Surgically-removed long clots are displayed according to the artery of origin.

DISCUSSION

Venous thrombosis and pulmonary embolism have been reported frequently in patients with COVID-19, but acute limb ischemia secondary to acute arterial thrombosis has been less commonly described. Studies have shown that hypercoagulability and endothelial damage in these patients are the main causes of thromboembolic events [8]. The presence of persistent lupus anticoagulation and high D-dimer levels in patients with COVID-19 increases the risk of associated thrombosis [9,10]. The remarkable incident about this patient was that he had an acute arterial thromboembolic accident despite being on therapeutic anticoagulation. Although the exact cause of this accident is unknown, the large thrombus (from the proximal common iliac artery to the distal leg arteries) may have been formed due to the increased coagulation status or endothelial damage secondary to COVID-19. Despite the normal results of coagulation tests or the administration of therapeutic anticoagulants, thrombotic events are likely in COVID-19 patients. Furthermore, during inflammatory storms, an increase in inflammatory mediators has been reported, which cannot be assessed by routine coagulation tests [6]. Immobility in critically ill COVID-19 patients can also lead to thrombotic events. The combination of these conditions with an increase in acute-phase reactants such as interleukin-6, which can cause endothelial damage and endothelial dysfunction, may justify the extensive thrombosis in the patient's arterial system [11]. However, it is interesting to note how the thrombosis occurred in the arterial system, where there is a high rate of blood flow, when it would

have been more logical for it to occur in the venous system, where the chance of blood stasis is higher. Anticoagulants are now an important treatment option for patients with severe COVID-19. The results of a study by Tang et al. [12] showed that the administration of heparin at a therapeutic dose reduced mortality by approximately 20% in patients with D-dimer levels greater than 3000 ng/mL over 28 days. Although starting anticoagulants has been shown to be beneficial in cases where the D-dimer level is six times higher than normal, it is unclear whether it will still provide additional benefits if higher doses are used [12]. In conclusion, it is not yet clear how thrombosis develops in critically ill patients with COVID-19. The occurrence of these complications while receiving anticoagulants in these patients indicates that the administration of anticoagulants cannot prevent acute arterial thrombosis. Therefore, the authors suggest that further research on the pathogenesis and management of COVID-19-induced hypercoagulable states should be conducted.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

ORCID

Pouya Tayebi
<https://orcid.org/0000-0002-6923-0221>
 Mahmoud Sadeghi Haddad Zavareh
<https://orcid.org/0000-0001-8701-7267>
 Gooya Tayyebi
<https://orcid.org/0000-0001-5516-0798>
 Fatemeh Zahra Abdollahi
<https://orcid.org/0000-0003-3885-3159>
 Fatemeh Mahmoudlou
<https://orcid.org/0000-0002-8251-9329>

AUTHOR CONTRIBUTIONS

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