Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Medical Imagery

A case of rapidly progressive upper limb ischemic necrosis in a patient with COVID-19

**ARTICLE INFO**

**Article history:**
Received 25 March 2021
Received in revised form 2 April 2021
Accepted 8 April 2021

**Keywords:**
COVID-19
Hypercoagulability
Thrombosis
Ischemia
Amputation

**ABSTRACT**

**Background:** For more than a year, health systems all over the world have been combating the global coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease was first described in the city of Wuhan in China, presenting as an atypical infection of the lower respiratory tract.

**Methods:** COVID-19 is characterized by multisystemic involvement, and mortality is attributed mainly to the respiratory system involvement, which may lead to severe acute respiratory distress syndrome and respiratory failure. Several COVID-19-associated complications are being increasingly reported, including arterial and venous thromboembolic events that may lead to amputation of the affected limbs. So far, a large number of reports have described hypercoagulability crises leading to amputation of the lower limbs. However, a search of the National Library of Medicine (MEDLINE) revealed no cases of urgent upper limb amputation in COVID-19 patients.

**Results:** This article describes a novel case of upper limb ischemia in a COVID-19 patient, with rapid progression to hand necrosis, requiring urgent through-arm amputation of the upper limb.

**Conclusions:** This case emphasizes the need for anticoagulant therapy in COVID-19 patients and to maintain a constant awareness of the possible thromboembolic COVID-19–related sequelae.

© 2021 The Author(s). Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

**Introduction**

Since December 2019, countries all over the world have been combating a global pandemic of a disease named coronavirus disease 19 (COVID-19), caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This disease was first described in a cluster of patients who presented with atypical pneumonia in Hubei Province in China. Up to March 18, 2021, approximately 122 million people had been affected by the novel coronavirus worldwide, with more than 2.6 million deaths.

The clinical presentation of COVID-19 falls within the spectrum of an asymptomatic condition to a rapidly progressive fatal disease, which may result from multi-organ failure, mainly involving the respiratory system. Common symptoms include high-grade fever, throat pain, loss of smell and taste sensations, dry cough, headache, and myalgia. Typical laboratory findings include elevated C-reactive protein, lymphopenia, and high D-dimer levels, which reflect an exuberant inflammatory process and endothelial injury. These processes are believed to be the etiology of the venous and arterial thromboembolic phenomena that frequently occur in COVID-19 patients (Ortega-Paz et al., 2021). In addition, renal function impairment and elevated liver enzymes are largely reported. Diffuse pulmonary infiltrates are the characteristic radiological findings observed in hospitalized patients. The diagnosis is confirmed by positive real-time reverse transcription PCR (RT-PCR) testing from nasopharyngeal swabs for SARS-CoV-2.

Treatment is based on supportive measures, oxygen supply, mechanical respiratory assistance, and systemic anti-inflammatory corticosteroids. Anticoagulants are widely used for the treatment or prevention of venous thromboembolism and hypercoagulability states that are increasingly reported in patients with COVID-19, apparently due to the inflammatory response and diffuse endothelial injury. The efficacy of antiviral and immunological preparations is controversial. Various antiviral vaccines are under development, and some are already in clinical use around the world. So far, several cases of COVID-19–associated lower limb ischemic injuries have been reported (Bellosta et al., 2020); however, no reports regarding ischemia of the upper limbs necessitating urgent upper limb amputation in COVID-19 patients have yet been published.

A case of severe upper limb ischemia with rapid progression to necrosis of the hand and the distal forearm in a COVID-19 patient, necessitating urgent amputation of the upper limb, is reported here.

**Case description**

A 50-year-old female, who tested positive for SARS-CoV-2 three days prior to her admission, was referred with fatigue, nausea,
abdominal pain, and elevated blood glucose measurements. Her past medical history was remarkable for hypertension, dyslipidemia, type 1 diabetes mellitus, and chronic kidney disease, and monoclonal gammopathy of undetermined significance. Her vital signs on admission were normal and a physical examination was unremarkable. She had normal peripheral arterial pulsations in her four limbs. Laboratory workup revealed hyperglycemia of 928 mg/dl, creatinine 8.3 mg/dl, pH 6.97, bicarbonate (HCO₃⁻) 6.2 mmol/l, and serum osmolality 385 mOsmol/kg. Serum sodium was 136 mmol/l, potassium 3.7 mmol/l, and anion gap 36 mEq/l. The D-dimer level was 3465 ng/ml.

A diagnosis of diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome overlap was made, and intravenous short-acting insulin together with fluid replacement was initiated. Clinical and laboratory improvements were observed, and the gastrointestinal symptoms resolved completely. Glucose values decreased to 122 mg/dl and blood pH improved up to 7.27. Bicarbonate increased to 23 mmol/l, creatinine decreased to 2.3 mg/dl (around known baseline values), and the anion gap normalized.

Three days following admission, the patient became drowsy and rapidly lost consciousness. Brain computed tomography was normal. Lumbar puncture revealed 154 mg/dl protein in the cerebrospinal fluid (CSF) and two monocytes, with no erythrocytes. CSF virology PCR testing was negative for SARS-CoV-2, herpes simplex virus type 1, varicella zoster virus, and enterovirus, and CSF cultures were sterile.

In addition, acute and rapidly progressive right hand swelling with ischemic signs was noticed. A physical examination revealed intact ulnar and radial pulses and an elongated capillary refill time. Finger puncture was not followed by bleeding. The patient’s left hand became slightly swollen with no ischemic signs (Figure 1), and both lower limbs were without signs of ischemia. A right hand computed tomography angiogram (CTA) demonstrated short thrombotic occlusion of the distal radial artery; however arterial supply through the palmar arch proved sufficient (Figure 2).

Evaluation of the digital arterial supply by CTA was non-conclusive. The patient was evaluated by vascular and orthopedic surgeons, and digital ischemia at the capillary level was believed to be taking place. Intravenous full-dose heparin combined with a synthetic analogue of prostacyclin (iloprost) was started, along with a smooth muscle relaxant vasodilator (papaverine) and a dihydropyridine calcium channel blocker (amlodipine). Testing for heparin-induced thrombocytopenia and anti-phospholipid antibodies were negative. Serum cryoglobulins were negative as well.

Due to the rapidly deteriorating severe ischemia with hand necrosis despite full-dose heparin treatment (Figure 3), a through forearm amputation of the right upper extremity was performed 2 days following the onset of symptoms. After the amputation, the amputee appeared well vascularized, and the left hand swelling did not deteriorate or appear ischemic.

**Literature review**

Current evidence implicates SARS-CoV-2 infection in hypercoagulable states, and several cases of arterial and venous atherothrombotic events have been reported so far. It has been postulated that endothelial injury due to invasion of the endothelial cells by the virus, which results in endothelial dysfunction, plays a central role in the hypercoagulability process (Teuwen et al., 2020; Lowenstein and Solomon, 2020). In addition, hospitalized patients with severe COVID-19 are mostly bedridden and immobile, which causes venous blood stasis and enhances the hypercoagulability state. Moreover, a number of changes in circulating prothrombotic factors have been postulated in COVID-19 patients, such as elevated Factor VIII, fibrinogen, and hyperviscosity states (Panigada et al., 2020; Maier et al., 2020).

Venous thromboembolism, including deep venous thrombosis (DVT) and pulmonary embolism, is common among acutely ill patients hospitalized with COVID-19, even when prophylactic anticoagulation is administered. A post-mortem study on individuals with COVID-19 revealed DVT in seven out of 12 (58%) patients (Wichmann et al., 2020). Likewise, cases of arterial thrombosis are being increasingly reported, including central nervous system involvement. In a study that included 3334 individuals (829 intensive care unit (ICU) patients and 2505 non-ICU patients), Bilaloglu et al. reported stroke in 1.6% and myocardial infarction in 8.9%. Risk factors for arterial thrombosis included older age, male sex, Hispanic ethnicity, history of coronary artery disease, and D-dimer >230 ng/ml on presentation (Bilaloglu et al., 2020).

![Figure 1](image1.png) **Figure 1.** The right (A) and left (B) hands, as seen on the day of symptom onset.
Similarly, de Roquetaillade et al. reported arterial thromboembolic events in 20 of 209 patients (9.6%) with COVID-19. It was emphasized that at the time of the ischemic arterial events, all of the affected patients were on anticoagulant treatment: 50% received a thromboprophylaxis dose and 50% received full-dose anticoagulation. The authors mentioned several publications that have described COVID-19 patients presenting with acute extremity pain, in the absence of significant respiratory symptoms, and concluded that mild COVID-19 cases may also present with significant prothrombotic complications (de Roquetaillade et al., 2021).

In accordance with the current case, Kaur et al. reported the case of a 71-year-old diabetic male who presented with severe COVID-19 pneumonia (Kaur et al., 2020). On day 5 of hospitalization, he experienced severe pain in his right arm, with documentation on Doppler ultrasound of an intraluminal thrombus within the right brachial and radial arteries. CTA showed a non-occlusive thrombus of the right brachiocephalic trunk and an occlusive thrombus in the axillary artery with reconstituted flow in the diminutive brachial artery extending to the radial, proximal ulnar, and interosseous arteries, and incomplete visualization of the distal ulnar artery. The patient received full-dose anticoagulant treatment and underwent open thromboembolectomy of the right brachiocephalic, subclavian, axillary, brachial, radial, and ulnar arteries, and endarterectomy of the right brachial artery, with a satisfactory outcome. The patient was maintained on therapeutic anticoagulation post procedure (Kaur et al., 2020).
Summary

In this paper, we have described a novel case of rapidly progressive acute upper limb ischemia, involving mainly the small capillaries of the hand in a female patient with COVID-19, resulting in an urgent amputation of her upper limb due to fulminant necrosis of the hand and distal forearm (Figure 3). This case emphasizes that it is highly recommended to include antithrombotic treatment in every hospitalized COVID-19 patient, unless an absolute contraindication exists, and raises the need for awareness of the medical staff for the possibility of venous and arterial hypercoagulability states, which frequently complicate patients with COVID-19, regardless of the severity of systemic or respiratory symptoms. Prompt and on-time diagnosis undoubtedly may save limbs or even the lives of patients with COVID-19.

Essentials section

The COVID-19 pandemic continues to challenge caregivers all over the world. Hematological complications are frequent and early diagnosis may be life-saving. Thromboembolic and hypercoagulability events may result in limb amputations and could even have a fatal outcome. Maintaining awareness and early diagnosis and treatment will minimize such untoward events and save the lives of COVID-19 patients.

Author contributions

KM, YS, SN, and SH wrote the manuscript. KM, YS, LAH, and SH were involved in the management of the patient. ML was involved in the radiological investigation and interpretation. SH and TH edited the final version of the manuscript.

Funding source

No funding was received for this work.

Patient consent

Consent was obtained from the patient regarding publication.

Conflict of interest

No conflict of interest to declare by any of the authors.

References

Bellosta R, Luzzani L, Natalini G, Pegorer MA, Attisani L, Cosso LC, et al. Acute limb ischemia in patients with COVID-19 pneumonia. J Vasc Surg 2020;72(December (6)):1864–72, doi:http://dx.doi.org/10.1016/j.jvs.2020.04.483 Epub 2020 April 29.
Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in hospitalized patients with COVID-19 in a New York city health system. JAMA 2020;324(8):799.
de Roquetaillade C, Chousterman BG, Tomasoni D, et al. Unusual arterial thrombotic events in Covid-19 patients. Int J Cardiol 2021;323:281.
Kaur P, Qaza F, Ramahi A, Shamoony S, Singhal M, Shamoony F, et al. Acute upper limb ischemia in a patient with COVID-19. Hematol Oncol Stem Cell Ther 2020;24:1039.e1039.e1039. Epub 2020 September 1.
Kuiper SL, Grothaus MM, Panigada S, et al. Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost 2020;18(7):1738 Epub 2020 May 25.
Maier CL, Truong AD, Auld SC, Polly DM, Tanksley CL, Duncan A. COVID-19-associated hypercoagulability: a link between inflammation and thrombophilia?. Lancet 2021;395(10239):1758 Epub 2020 November 24.
Panigada M, Bottino N, Tagliafuca P, Grasselli G, Novembrino C, Chantarangkul V, et al. Hypercoagulability of COVID-19 patients in intensive care unit: a report of thromboelastography findings and other parameters of hemostasis. J Thromb Haemost 2020;18(7):1738 Epub 2020 June 24.
Teuwen LA, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. Nat Rev Immunol 2020;20(7):389.
Wichmann D, Sperhake JP, Lütgert H, Meyer S, Niederle B, Heimans H, et al. Symptomatic and asymptomatic COVID-19 patients have acute and chronic hypercoagulability: an international prospective cohort study. Blood 2021;137(2):e20201420147 Epub 2020 May 6.
Kamal Makhoula a, Yousef Shukha a, Lan Abu Hanna b, Samy Nitecki d, e, Maxim Leiderman a, Tony Hayek a, e, Shadi Hamoud a, c, d, e, f, *
 a Internal Medicine E and Keter B Departments, Rambam Health Care Campus, Haifa, Israel
 b Department of Vascular Surgery, Rambam Health Care Campus, Haifa, Israel
 c Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel
 d Department of Medical Imaging, Rambam Health Care Campus, Haifa, Israel

* Corresponding author at: Internal Medicine E and Keter B Departments, Rambam Health Care Campus, Haifa, Israel.
E-mail address: s_hamoud@rmc.gov.il (S. Hamoud).

Received 25 March 2021
Received in revised form 2 April 2021
Accepted 8 April 2021