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.

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Letter to the Editor

Stroke as a delayed manifestation of multi-organ thromboembolic disease in COVID-19 infection

Dear Editor,

Here, we report a patient with COVID-19 with delayed onset multivessel cerebral infarcts and systemic pro-thrombotic state and coagulopathy manifesting as acute limb ischemia and pulmonary embolism to highlight the importance of vigilant monitoring for neurologic impairment and coagulopathy in patients with severe cases of COVID-19 infection. In December 2019, a cluster of pneumonia cases emerged in Wuhan, Hubei Province; later identified as a novel severe acute respiratory syndrome coronavirus (SARS-CoV-2), also known as coronavirus disease 2019 (COVID-19). The virus has spread globally with subsequent designation as a pandemic by the World Health Organization. Clinical manifestations encompass numerous systems, including pulmonary, renal, gastrointestinal, hepatic, but more recently, neurologic, cardiovascular, and hematologic domains [1]. Guidelines for the management of the neurologic and hematologic complications of COVID-19 are under development.

A 72-year-old woman with a past medical history significant for hypertension, diabetes, chronic renal failure, and gout presented with 3 weeks of progressive cough, general myalgia, and shortness of breath. On presentation, she was hypoxic and tachypneic with evidence of wheezing with abnormal lung sounds, but normal neurological examination. Laboratory tests showed leukocytosis, acute kidney injury, transaminitis, and rhabdomyolysis. Elevated C-reactive protein and ferritin were detected. Chest X-ray revealed bilateral patchy airspace opacities, consistent with multifocal pneumonia. The patient was initiated on vancomycin, cefepime and azithromycin. She was confirmed to have a positive COVID-19 PCR-based test, consistent with infection. Hydroxychloroquine could not be started due to a quinine allergy and prolonged QTc interval.

On days 3 and 4 of admission, the patient developed acute hypoxic respiratory failure and septic shock, requiring intubation and vasopressor support. The patient's condition continued to decline with persistent bilateral pneumonia, worsening renal failure with uremia, acidosis and hyperkalemia requiring dialysis and lymphopenia. The patient had a repeat COVID-19 test with positive result. A head CT without contrast did not reveal acute pathology.

On day 7, the patient was noted to have bilateral light blue or purple skin mottling of both feet with palpable left dorsalis pedis pulse (Fig. 1a and b). The patient did not have a baseline coagulation profile on admission, but, on day 7, a prolonged prothrombin time (PT) and elevated INR were noted (PT 13.5 s (normal: 9.4–11.7); INR 1.32 s (normal: 0.90–1.13)), along with a normal activated partial thromboplastin time (aPTT) of 28.5 s (normal: 23.1–33.1), and platelets (146,000/mm^3, normal: 150–450,000/mm^3) prior to transitioning from subcutaneous heparin prophylaxis to intravenous heparin infusion due to concerns of COVID-19 related microvascular disease. No antiplatelet or therapeutic anticoagulation were given prior to onset of embolic disease. The patient then developed an unstable ventricular tachycardia, which resolved after synchronized cardioversion. Transthoracic echocardiogram showed right ventricle dilation and free wall hypokinesis with spared apical contractility (McConnell's sign), suggesting acute pulmonary embolism.

On day 10, neurological examination revealed a Glasgow Coma Scale of 3 (E1VtM1). Pupils were symmetric and reactive to light bilaterally, no obvious facial asymmetry was noted, and oculocephalic and cough reflexes were preserved. Non-contrast head CT obtained revealed bilateral cerebral infarcts in multiple vascular territories including cortical and subcortical regions (Fig. 1c and d). Serial blood cultures due to persistent fever were unrevealing.

Due to high mortality risk with predicted poor functional outcome, the patient's code status was changed to do-not-resuscitate after discussion with family members. On day 11, the patient's blood pressure and heart rate continued to drop despite maximal cardiovascular support, and the patient died after cardiopulmonary arrest. The coagulation profile on day of expiration showed aPTT 51.8 s, PT 16.1 s, INR 1.60 s, fibrinogen 557 mg/dL (normal: 186–466), D-dimer 10.26 mg/L (normal: < 0.50), and platelet count 206,000/mm^3. Of note, full work up including duplex ultrasound of all limbs, CT pulmonary angiogram and bubble study were pending at the time of death.

Organ involvement of COVID-19 is recognized to extend well beyond the respiratory tract, including neurologic involvement [1]. Systemic coagulation alterations have been reported [2,3], leading to vascular conditions, including stroke [4–6]. Cerebrovascular diseases has been reported as a presenting syndrome in both young and older patients with COVID-19 presenting with acute stroke symptoms [4–6]. The overall incidence of stroke in hospitalized or severely ill patients afflicted with COVID-19 has ranged from 0.9–5.7% [5,6]. Deep-vein thrombosis, pulmonary embolism and myocardial infarctions have also been reported [2,3].

Increased D-dimer, fibrinogen degradation products and other coagulopathies are common in severely ill COVID-19 patients and are associated with poor outcome [2,3,7]. Activated partial thromboplastin time and prothrombin time have also been reported, but are less frequent [2]. Anticoagulation treatment, particularly low molecular weight heparin, has been recommended due to benefits in reducing mortality and anti-inflammatory properties in patients with sepsis-induced coagulopathy scores ≥ 4 and D-dimers > 6-fold of upper limit of normal (3.0 μg/ml) [2,8,9]. However, full anti-coagulation is not routinely recommended [2,10]. Of note, our patient was fully anticoagulated prior to development of her stroke. Antiphospholipid antibodies have been associated with COVID-19-related strokes in some reports, but their role remains under active investigation [10].

In our report, an elderly patient with significant comorbidity burden was hospitalized initially with respiratory symptoms and bilateral multifocal pneumonia from COVID-19 that rapidly progressed to cause severe sepsis, septic shock, micro- and macro-vascular thrombotic phenomena, and evidence of hypercoagulability, leading to multi-vessel

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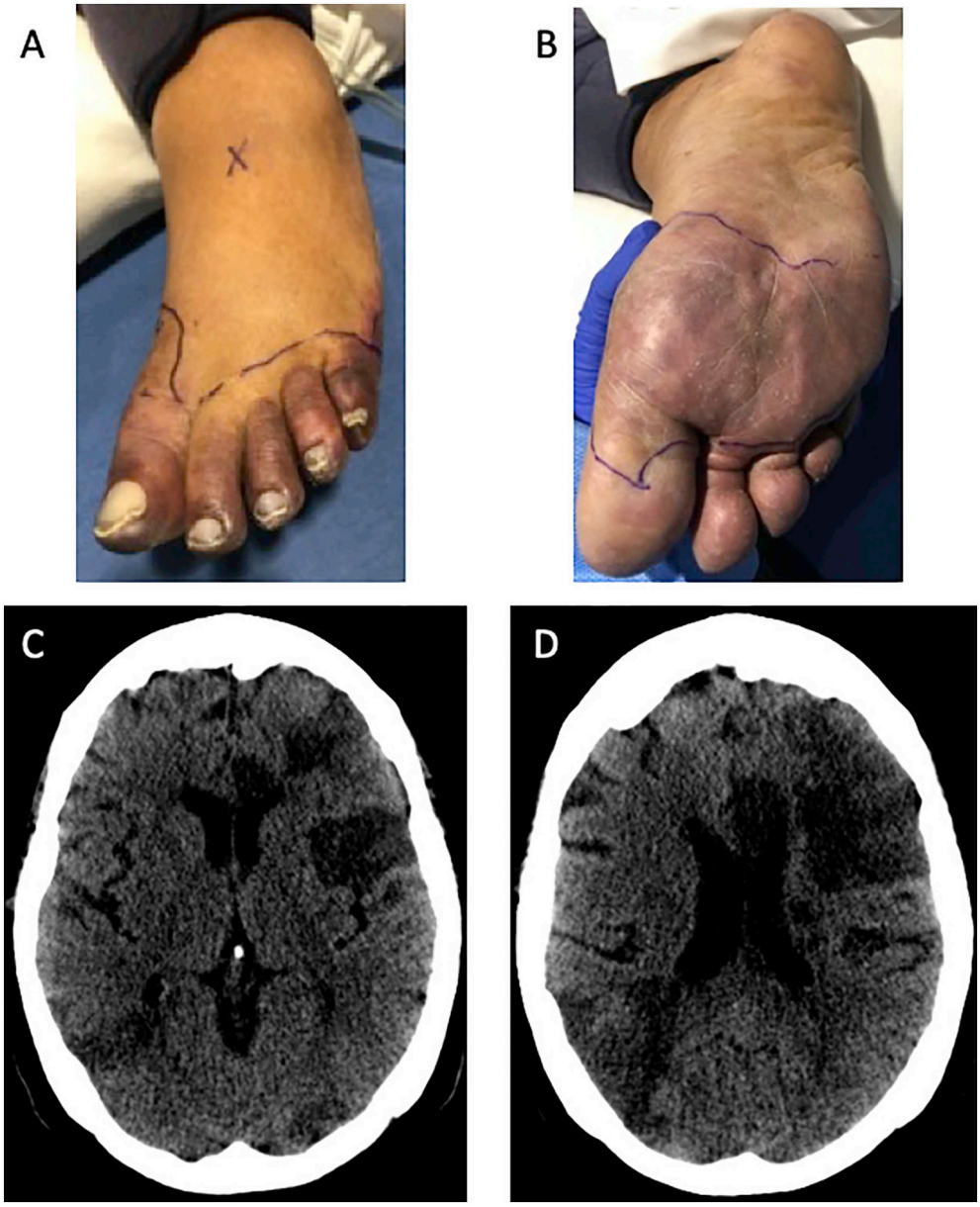

Fig. 1. Stroke and systemic thromboembolic manifestations of COVID-19. (A, B). Limb ischemia. The patient was noted on day 7 of hospitalization to have developed bilateral foot ischemia. **(C, D).** Cranial imaging revealed multiple cerebrovascular territory infarcts.

stroke. Despite the recognition of these issues, current guidelines for managing stroke risk in patients afflicted with COVID-19 are evolving in management of hypercoagulation [2]. Given the reports of COVID-19 patients succumbing suddenly after infection, along with unexpected lethal and poor functional outcome events (e.g. cerebrovascular accidents and pulmonary emboli), early anticoagulation and vigilant neurological monitoring and management, especially in critically ill COVID-19 patients, should be considered for possibly preventing and reducing mortality and morbidity in patients. Larger scale studies investigating the benefit of anticoagulation while balancing its risks are necessary to guide management of hypercoagulability.

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