Delayed manifestation of COVID-19 presenting as lower extremity multilevel arterial thrombosis: a case report

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Received 9 June 2020; first decision 7 July 2020; accepted 10 September 2020; online publish-ahead-of-print 19 November 2020

Background
Venous thrombo-embolic events have been described in hospitalized patients with coronavirus disease 2019 (COVID-19), suggesting the presence of coagulopathy induced by the viral infection. To date, only rare cases of arterial thrombosis related to COVID-19 have been reported.

Case summary
A 54-year-old patient with an influenza-like illness 15 days earlier, which resolved, and no known cardiovascular risk factor presented with acute right lower limb ischaemia. A computed tomography angiogram of the abdominal aorta and lower extremities showed, in the absence of vascular disease, a subocclusive thrombosis of the right common iliac artery and an occlusion of the right internal iliac, profunda femoral, and popliteal arteries. On the left side, the computed tomography angiogram demonstrated a non-occlusive thrombosis of the common femoral artery. The patient underwent emergency surgical thrombectomy as well as endovascular revascularization on the right side followed by therapeutic anticoagulation, with normalization of the limb perfusion. A nasopharyngeal swab for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by real-time reverse transcription–PCR (rRT–PCR) was negative three times. Haemostasis analysis showed a mild hyperfibrinogenaemia and a shortening of the activated partial thromboplastin time. An extensive screening for cardio-embolism was negative. As the thrombotic event was unexplained, antibody testing for SARS-CoV-2 was performed and the result was positive.

Discussion
Venous thrombosis and pulmonary embolisms have been observed in COVID-19. As in our case, the first reports on COVID-19-associated arterial thrombotic events have emerged. A better understanding of the coagulopathy in COVID-19 is essential to guide prevention and treatment of venous as well as arterial thrombo-embolic events.

Keywords
Arterial thrombosis • COVID-19 • Acute limb ischaemia • Coagulopathy • Case report
Learning points

- Novel coronavirus disease 2019 (COVID-19) may be responsible for arterial thrombosis in affected patients, in addition to venous thrombo-embolic events.
- Thrombo-embolic manifestations would appear to be the result of a procoagulant state promoted by the viral infection.
- Clinicians need to be aware of these manifestations because of their severity.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), most of the time presents as an upper respiratory influenza-like illness, which can progress to pneumonia and, in a minority of cases, to acute respiratory distress syndrome (ARDS) and multiorgan failure. In addition, a coagulation disturbance, associated with an increased risk of venous thrombosis and pulmonary embolism with a range of 4.4–8.2% in hospitalized COVID-19 patients, has been reported.\(^2\)\(^,\)\(^3\)\(^–\)\(^7\) Lately, a few cases of peripheral arterial thrombosis related to COVID-19 disease have been described.\(^2\)\(^,\)\(^5\)\(^–\)\(^7\) We report the case of a 54-year-old man who presented with acute arterial ischaemia of the right lower limb due to multilevel arterial thrombosis as a delayed manifestation of COVID-19.

Timeline

| Day 0 | Presentation to the emergency department with acute right lower limb ischaemia. CT angiogram of the aorta and lower limbs demonstrated the presence of multilevel arterial thrombosis. Nasopharyngeal swab with rRT–PCR for SARS-CoV-2 was negative. |
| Day 0 | Emergency vascular surgery with arterial embolectomy. |
| Day 2 | Below-the-knee endovascular intervention due to distal embolization post-surgery, followed by a healing of critical ischaemia. |
| Day 24 | Negative lupus anticoagulant blood test. |
| Day 8 | Anti-SARS-CoV-2 serologies were positive. |
| Day 11 | The recommended overall assessment did not reveal an aetiology responsible for the acute ischaemia of the lower limb. Discharged home on anticoagulation with vitamin K antagonists for 3 months. |
| Day 3 | Positive lupus anticoagulant blood test. |
| Day 4 and 8 | Repetition of nasopharyngeal swab tests for SARS-CoV-2 by rRT–PCR, returning negative each time. |
| 4 days prior to presentation | Pain and coldness of the right foot. |
| 18 days prior to presentation | Contact with a SARS-CoV-2-infected colleague, followed by flu-like symptoms, with a dry cough, anosmia, and ageusia for 1 week. |

Case presentation

A 54-year-old man presented to the emergency department because of a pain and coldness of the right foot lasting for 4 days. The pain was not improved by standing. He was obese (body mass index of 32.4 kg/m\(^2\)), had no previous medical history, and no cardiovascular risk factors. In particular, he never smoked. In addition, he was not taking medications or illicit drugs and had an occasional consumption of alcohol. He did not have prior symptoms suggestive of lower limb arterial insufficiency. On admission, the patient reported hypoaesthesia and weakness of the right foot in the absence of paraesthesia. Eighteen days earlier, he developed flu-like symptoms, a dry cough, anosmia, and ageusia, all of which was resolved after a week. On admission, he was slightly hypertensive (143/88 mmHg), tachycardic (109 b.p.m.), tachypnoeic (26/min), and afebrile (37.4°C). On clinical examination, the right femoral pulse was weakened, and more distal pulses in the right leg were absent. There was a marked thermal gradient at the level of the right knee, with a livedo below the knee and at the level of the foot. The skin recoloration time on the foot was >10 s. The hypoaesthesia and paresis of the right foot that the patient complained of were found on physical examination. Examination of the contralateral lower limb as well as of the upper limbs was unremarkable. Cardiac auscultation revealed regular tachycardia with no audible murmur. The rest of the examination was normal. The electrocardiogram showed sinus tachycardia, in the absence of other abnormalities.

Blood tests showed a slight leukocytosis (13.6 \(\times\) 10\(^9\)/L; normal range 4–11 \(\times\) 10\(^9\)/L), an increased C-reactive protein (24.40 mg/L; 0–10 mg/L), hyperkalaemia (5.3 mmol/L; 3.6–4.6 mmol/L), hyperglycaemia (19.1 mmol/L; 4.1–6 mmol/L), and a mild increase in creatinine kinase (369 U/L; 47–222 U/L). Fibrinogen was mildly increased (4.2 g/L; 1.5–3.5 g/L), activated partial thromboplastin time was slightly below the norm at 24.4 s (22–37 s), and platelet count was normal. In view of the strong clinical suspicion of lower limb arterial thrombosis, and according to the institutional protocol, D-dimer levels were not measured and a computed tomography angiogram (CTA) of the abdominal aorta and the lower limbs was performed, showing a subocclusive suspended thrombosis of the right common iliac artery, and an occlusion of the right internal iliac artery, profunda femoral artery, and popliteal artery, without outflow below the knee (Figure 1). On the left limb, the CTA demonstrated a non-occlusive thrombosis of the common femoral artery. On CTA there was no evidence of vascular disease; in particular no calcifications or atherosomatous lesions were identified. Testing for SARS-CoV-2 by real-time reverse transcription–PCR (rRT–PCR) with a nasopharyngeal swab performed in the emergency department was negative. This swab was done 18 days after the onset of flu-like symptoms, and the patient had no symptoms related to an upper airway infection at that time of testing.
He was treated by emergency surgical embolectomy, followed by below-the-knee endovascular intervention due to distal embolization post-surgery, as well as therapeutic anticoagulation, with normalization of the limb perfusion.

A complete cardiovascular assessment consisting of echocardiography, cardiac magnetic resonance imaging, and Holter monitoring could not identify sources of embolism. Carotid and vertebral Duplex ultrasound showed no evidence of vascular disease. Type 2 diabetes was newly diagnosed and required treatment with insulin. Nasopharyngeal swabs for SARS-CoV-2 by rRT–PCR were performed three times in total, each of them returning negative. Nevertheless, based on the high clinical suspicion and the unexplained arterial thrombosis, a SARS-CoV-2 antibody test was performed, which was strongly positive with IgG (index value: 11.18; >1) and IgA (index value: 13.88; >1), confirmed by immunofluorescence assay. An antibody test for lupus anticoagulant was initially positive but turned negative thereafter. At day 11, the patient was discharged home on vitamin K antagonist (VKA)-based anticoagulation.

**Discussion**

We reported acute lower limb ischaemia due to arterial thromboses as a delayed manifestation of COVID-19. While venous thrombosis and pulmonary embolism have been reported on multiple occasions in COVID-19,¹⁻³ to our knowledge only six cases of peripheral arterial thrombosis presumed related to COVID-19 have been documented.²⁻⁷ The arterial territories involved were the infrarenal aorta with extension to the common iliac arteries, the brachiocephalic trunk with involvement of the axillary artery, the arteries of the lower limbs, the thoracic aorta, the mesenteric artery, and the jejunal artery.²⁻⁸

Regarding the thrombo-embolic events observed in COVID-19, an underlying coagulopathy is strongly suspected. There is evidence that viral infections may be responsible for coagulation imbalance, leading to an overall prothrombotic risk.⁹ Increased von Willebrand factor and expression of tissue factor and Toll-like receptors have been shown to contribute to the procoagulant state.⁹ A prospective multicentre study showed that patients with ARDS secondary to COVID-19 had more venous thrombotic complications compared...
with non-COVID-19 patients with ARDS. Interestingly, the activities of von Willebrand factor, von Willebrand antigen, and factor VIII were significantly increased in COVID-19 patients. Delayed fibrinolysis has also been reported in COVID-19, especially in the setting of ARDS. In addition, one study on COVID-19 patients admitted to intensive care units showed that the vast majority had positive lupus circulating anticoagulant. The degree of elevation of this antibody encountered in COVID-19 was more pronounced than in other viral infections and could be the consequence of significant cell destruction. The lupus anticoagulant was transiently positive in our patient. However, the interpretation of this result is limited, due to the acute inflammatory state and the presence of heparin anticoagulation, which may cause falsely elevated levels of these antibodies.

Regarding our patient, it is interesting to point out that three searches for SARS-CoV-2 by rRT–PCR came back negative, and only antibody detection was able to confirm the diagnosis. With respect to the arterial thrombotic events, the lack of arterial disease on imaging as well as the lack of cardiovascular risk factors other than the newly diagnosed diabetes strongly suggests the association with COVID-19. In fact, although diabetes can cause arterial thrombosis as a result of atherosclerotic plaque fissures/ruptures, our patient has no imaging evidence of arterial disease. The patient complained of right lower extremity pain 15 days after the onset of symptoms to arterial thrombotic manifestations of 14 days. This finding corresponds well with previous reports showing a median time from COVID-19 disappeared. This finding corresponds well with previous reports showing a median time from COVID-19.

In conclusion, it is critical that healthcare workers caring of patients with COVID-19 or recovering from COVID-19 are aware of this complication, which can have catastrophic consequences for the patient. Studies on the role of coagulopathy in venous as well as arterial thrombus formation in COVID-19 are needed.

Lead author biography

Dr Frédéric Glauser is the director of the Interventional Angiology Unit of the University Hospitals of Geneva. After completing his MD in Geneva, he trained in Angiology in the Centre Hospitalier Universitaire Vaudois (CHUV) and completed a clinical fellowship in Bad Krozingen. He has a particular expertise in the interventional treatment of peripheral arterial disease.

Acknowledgements

The authors thank Alessandro Casini for his contribution and proof-reading of this manuscript.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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