Severe arterial thromboembolism associated with COVID-19 infection

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Abstract:

Purpose: The purpose of our report is to present two patients with acute peripheral arterial thrombosis as a result of COVID-19 infection and discuss the unique features of arterial thrombosis in patients suffering from COVID-19.

Case Report: We present a 66-year-old female and a 53-year-old male with proven COVID-19 infection who developed acute lower limb ischemia. Common features in both patients were a multi-segment arterial occlusion in previously healthy arteries, developing despite prophylactic anticoagulation about 15 days after the onset of COVID-19 symptoms. Limb salvage was achieved by early diagnosis and expedited thrombectomy.

Conclusion: COVID-19 associated arterial thromboembolism has several unique features reflecting the underlying pathogenetic mechanism which involves a combination of coagulopathy and endothelial dysfunction. Clinical vigilance allowing early diagnosis and expedited surgery remains the key to a successful outcome.

INTRODUCTION

To date, COVID-19 pandemic has affected more than 153 million people worldwide and caused more than 3.2 million deaths.[1] Pneumonia, acute respiratory distress syndrome (ARDS), acute liver injury, acute cardiac injury, secondary infection, acute kidney injury, septic shock and venous thromboembolism are the most common complications. Several reports of peripheral arterial thrombosis have also been published, highlighting the need for prophylactic or even therapeutic anticoagulation and the increased amputation risk.[2-5] Herein we present two patients with acute peripheral arterial thrombosis as a result of COVID-19 infection and discuss the unique features of arterial thrombosis in patients suffering from COVID-19.

CASE 1

A 66-year-old woman with a history of hypertension, type 2 diabetes mellitus, dyslipidemia and cervical spinal fusion surgery presented to Vostanio General Hospital of Mytilene with severe dyspnea, chest pain and fatigue. The symptoms had started a week before and worsened sharply on the eighth day. Physical examination revealed bibasilar crackles and chest X-ray showed bilateral infiltrates. Oxygen saturation (SpO_2) was 88% on room air, partial pressure of oxygen (pO_2) 61 mmHg and of carbon dioxide (pCO_2) 44 mmHg. Nasopharyngeal polymerase chain reaction (PCR) testing for COVID-19 was positive. The patient was admitted to the COVID-19 unit and received remdesivir, dexamethasone, ceftriaxone, and enoxaparin 40 mg bid. To maintain an SpO2 of 92%, the patient required supplemental oxygen administered initially with a fraction of inspired oxygen (FiO2) of 50% by venturi mask, then with 100% FiO_2 by non-rebreather mask and thereafter with high flow nasal cannula (HFNC) and high velocity nasal insufflation. Ten days after her admission to the hospital, the patient developed acute right lower limb ischemia with pain, paralysis and paresthesia below the knee, while physical examination revealed cyanosis, coldness and absence of palpable pulses at the femoral artery and below. A computed tomography angiography (CTA) showed partial thrombosis of the right common iliac artery and complete thrombosis of the right profunda femoral artery, right popliteal artery and the right posterior and anterior tibial arteries (Figure 1). The only patent arterial segment at the calf was the distal third of the peroneal artery. There was no sign of atherosclerotic disease. The patient was intubated and transferred to Attikon Hospital by airplane in a negative pressure isolation chamber.

Upon arrival at Attikon Hospital, her white blood cells were 27,770/μl (89.6% neutrophils), platelets 504,000/ml, C-reactive protein79.4 mg/L, fibrinogen 486 mg/dl, d-dimers 7,273

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ng/ml, ferritin 1,270 ng/ml, LDH 770 U/L and interleukin-6 (IL-6) 265 pg/ml (normal range <7.0 pg/ml). The patient was taken to the operating room where the right femoral artery was exposed and thrombectomy was performed using a Fogarty catheter both proximally and distally. Thrombectomy was successful with immediate improvement of limb perfusion. The patient was transferred to the ICU and received enoxaparin at a dose of 80 mg bid. She was extubated after two weeks and discharged from the hospital after another two weeks. She was prescribed tinzaparin 4,500 IU od for one month and aspirin 100 mg od for indefinite time.

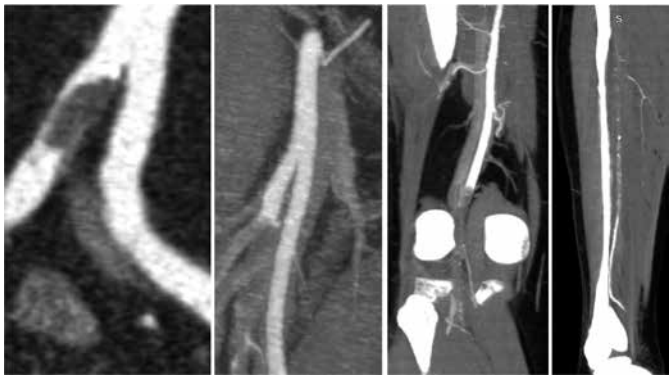

Figure 1: CTA of the aorta and the lower limbs depicting partial thrombosis of the right common iliac artery and complete thrombosis of the right profunda femoral, right popliteal and the right posterior and anterior tibial arteries.

CASE 2

A 53-year-old male presented to the emergency department of the "Attikon" Hospital reporting fever over the past 8 days and shortness of breath. He had already tested positive for COVID-19 by PCR in an external lab. Physical examination revealed bibasilar crackles, whereas blood gas testing showed severe hypoxemia, with an SpO2 of 87% on room air and a pO2 of 62 mmHg.

He was admitted to the COVID-19 unit and treated with dexamethasone, ceftriaxone, azithromycin, remdesivir and enoxaparin 40 mg bid. He was also placed in HFNC (60L - FiO2 95%), with satisfactory oxygenation. A chest CT scan revealed multiple diffuse infiltrates and ground-glass opacity occupying approximately 60-70% of the total pulmonary parenchyma (Figure 2).

During his treatment he remained afebrile and hemodynamically stable but unable to be weaned from high oxygen mixtures. On the 8th day of his hospitalization, he developed acute pain in his left lower extremity. Physical examination revealed reduced mobility and sensation of the left lower extremity, with tenderness, coldness and absence of palpable pulses in the popliteal, posterior tibial and dorsalis pedis artery. A CTA of the aorta and the lower limbs showed partial thrombosis of the aorta and complete thrombosis of the left profunda femoral, left popliteal artery, tibioperoneal axis and left anterior tibial artery (Figure 3). His white blood cells were 13,800/μl (92% neutrophils), platelets 306,000/ml, C-reactive protein79.5 mg/L, fibrinogen 606.4 mg/dl, d-dimers 606.4 ng/ml, ferritin 1,085 ng/ml, LDH 820 U/L and interleukin-6 (IL-6) 148 pg/ml. The patient was transferred to the operating room, where his left femoral artery was exposed and thrombectomy was performed using a Fogarty catheter with immediate restoration of limb perfusion. Rethrombosis occurred 6 hours later with recurrence of symptoms. The patient was taken to the operating room once again and was submitted to redo thrombectomy. He was placed on enoxaparin 80 mg bid and his further postoperative course was uneventful. Mobility and sensation were restored and his lung function gradually improved. He was discharged from the hospital 12 days after his thrombectomies, on tinzaparin 4,500 IU od for one month and aspirin 100 mg od as a long-term antithrombotic regimen.

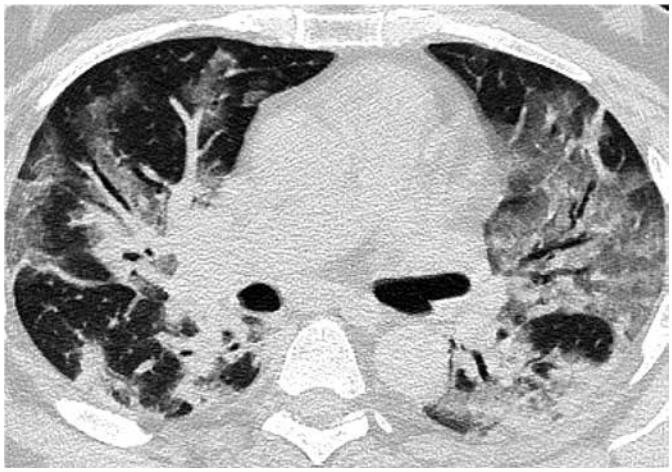

Figure 2: Chest CT revealing multiple diffuse infiltrates and ground-glass opacity occupying approximately 60-70% of the total pulmonary parenchyma.

Figure 3. CTA of the aorta and the lower limbs depicting partial thrombosis of the aorta and complete thrombosis of the left profunda femoral artery, left popliteal artery and tibioperoneal axis and left anterior tibial artery.

DISCUSSION

Our report highlights several unique features of COVID-19-associated arterial thrombosis. First, thrombosis affects several segments of the arterial tree of the lower limbs with the arteries between the affected segments remaining patent. Several authors have also described the simultaneous presence of thrombus in the thoracic or abdominal aorta and in some

of the iliac arteries (common, internal or external), some of the femoral arteries (common, deep or superficial), the popliteal or the crural arteries.[6-8] In our patients, CTA disclosed a nonocclusive thrombosis of the abdominal aorta (Case 2) or the common iliac artery (Case 1) and complete thrombosis of the deep femoral and the popliteal artery. The simultaneous presence of thrombi in multiple arterial segments raises the question of whether these are simultaneous thromboses or multiple emboli originating from the nonocclusive proximal thrombus. In this context, "COVID-19-associated arterial thromboembolism" might be a more appropriate term than "COVID-19-associated arterial thrombosis".

Another unique feature of COVID-19-associated arterial thrombosis is that it occurs in arteries with no sign of atherosclerosis and in patients without any previous severe comorbidities, risk factors for atherosclerosis or known cardiovascular disease.[5,7] This fact facilitates thrombectomy minimizing the risk of arterial injury by the Fogarty catheter and increasing the probability of technical success. COVID-19-associated arterial thrombosis might thus represent an exception to the general rule of vascular surgery, according to which thrombectomy is hardly ever a stand-alone procedure. The underlying cause of arterial thrombosis, which is almost always a high-grade stenosis, must be identified and treated. In COVID-19 disease, however, thrombosis is due to a combination of coagulopathy and endothelial dysfunction caused by a dysregulated immune response, with no underlying arterial lesion.[9,10]

Technical success and limb salvage, on the other hand, is greatly reduced in severely ill patients who are intubated in the Intensive Care Unit since, in such cases, diagnosis of limb ischemia will most probably be delayed. This may explain the great thrombus burden and the increased rate of amputation reported by some authors, as well as the high rate of primary amputation due to irreversible limb ischemia reported by some others.[1-5,11,12] This may also explain the good outcome in both of our patients who were in a good enough general condition to report the symptoms of limb ischemia as soon as they appeared.

Another interesting feature of COVID-19-associated arterial thrombosis is that it may occur despite the use of prophylactic low molecular weight heparin. This has been already described in the literature and is further supported by our report.[3,5,12] Not only did both of our patients receive prophylactic anticoagulation with LMWH at the time of arterial thrombosis but in intermediate doses as well (enoxaparin 40 mg twice daily).

The time interval between the onset of COVID-19 symptoms and the development of acute limb ischemia was 16 and 18 days in our patients. This finding is in accordance to the time interval reported in the literature, which is about 15 days,[3,8,12,13] although arterial thrombosis on day 4 or 5 has also been reported.[3,4]

The risk of thrombosis in COVID-19 patients has prompted several scientific societies to issue clinical practice guidelines, which are mostly targeted against venous thromboembolism. All of them recommend prophylactic dose LMWH in all patients who require hospital admission, whereas extended thromboprophylaxis should be considered after hospital discharge.[14,15] There has not been any recommendation against arterial thrombosis so far and the use of aspirin has not been studied. DOACs, on the other hand, should be withheld from patients with COVID-19 infection treated with antiviral drugs since an alarming increase in DOAC plasma levels has been observed in such cases.[16] DOACs can be safely used after discharge and have been actually reported to be the most commonly administered postoperative anticoagulation regimen in patients with arterial thrombosis treated at Mount Sinai Hospital.[17]

Surgical thrombectomy represents the most commonly applied treatment for COVID-19 associated arterial thrombosis, followed by catheter directed thrombolysis or mechanical thrombectomy, whereas a hybrid approach with surgical thrombectomy plus balloon angioplasty or stenting is reserved for the rare cases of acute thrombosis superimposed over atherosclerotic occlusive disease.[17-20] The lack of underlying atherosclerotic disease and the need for immediate restoration of blood flow, due to the presence of a neurologic deficit, made us chose surgical thrombectomy in both of our patients. The first patient was already intubated, whereas the second patient was treated under local anesthesia. The use of local or regional anesthesia is preferable in COVID-19 patients to prevent the risk of aerosolization of airway secretions.[21]

CONCLUSION

COVID-19 associated arterial thromboembolism has several unique characteristics including multi-segment involvement in previously healthy arteries, developing despite prophylactic anticoagulation about 15 days after the onset of COVID-19 symptoms. Although of utmost importance, preventive measures are limited by our inadequate understanding of the underlying pathophysiology of thrombus development in an artery without significant atherosclerosis. Clinical vigilance allowing early diagnosis and expedited surgery remains the key to a successful outcome.

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