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Case Report

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Limb Salvage after Covid-19 Related Major Arterial Thrombosis in an 81 -Year Lady with Critical Limb Ischemia: A Case Report

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ABSTRACT

Hypercoagulable state and thromboembolic events are common extra-pulmonary complications of COVID-19 that are increasingly reported in the literature. Unfortunately unlike VTE, no remarkable data are available on arterial thrombosis in SARS-CoV2 infected patients, and despite the use of anticoagulant and antiplatelet therapies, severe arterial thrombotic complications are observed. The objective of this case study is to share our experience about COVID-19 related peripheral arterial thrombosis and highlight the management plan of the resulting CLI in an elderly patient.

It is a case report of an 81- year lady that developed fever, vomiting, and bone aches for 3 days before being transferred to the fever hospital with gastrointestinal upset, where she was admitted to normal ward and the diagnosis of COVID-19 was confirmed by RT-PCR. The patient improved and discharged to home after one week, 5 days later she started to complain of painful right foot then the pain involved the whole leg later on with fixed color changes and coldness, however, the diagnosis of acute ischemia was missed for one week more until the patient came to our department, and arterial duplex revealed extensive thrombosis of the SFA, popliteal and tibial arteries with CLI (ABI was<0.4). The patient was prepared for prompt vascular intervention and surgical embolectomy was performed via combined popliteal and femoral approaches. A long, thick, more gelatinous and darker thrombus was retrieved both proximally and distally. The limb was saved with fairly good distal runoff. Unfortunately, one week after the operation the patient slipped and developed fracture neck femur of the same limb, and she was operated on one month later. The patient had uneventful postoperative course, and such lucky 81years lady kept a viable well-functioning limb and could walk again.

In conclusion, the key points of our case study include vigilant consideration of the arterial thrombosis in COVID-19 infected patients, routine monitoring of D-dimer levels with initiation of full-dose anticoagulation if levels elevated by six times the upper limit of normal, as well as prompt diagnosis of ALI, and urgent surgical revascularization to save the limb.

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Introduction

Coronavirus disease 2019(COVID-19) is a highly infectious disease of the human respiratory system caused by a newly discovered enveloped RNA B-coronavirus named severe acute respiratory syndrome coronavirus 2(SARS-CoV-2), and considered as a multi-organ disease. Such global pandemic is inflicting significant morbidity and mortality and has been declared by the World Health Organization as a public health emergency of international concern [1].

Hypercoagulable state and thromboembolic events are common extra-pulmonary complications of COVID-19 that are increasingly reported in the literature. Unfortunately unlike VTE and cardiovascular complications, no remarkable data are available on arterial thrombosis in SARS-CoV2 infected patients, and despite the use of anticoagulant and antiplatelet therapies, severe arterial thrombotic complications are observed [2, 3]. These thrombotic events are attributed to various cellular and molecular mechanisms, including platelets activation, triggering the coagulation cascade, the formation of neutrophil extracellular traps (NETs) and cytokine storm syndromes [4, 5]. Some studies noticed an unusual severity of lower limb ischemia and unusual extension or localization of arterial thrombosis diagnosed in a short period of time.

By review of the current literature, arterial thrombosis occurred in approximately 4.4% of critically ill COVID-19 patients. Males, elderly, and patients with co- morbidities were the most; the disease was symptomatic in >95% of cases and involved multiple arteries in approximately 18% of patients. The anatomical distribution of the arterial thrombotic events was reported as follows: limb arteries (39%), cerebral arteries (24%), great vessels (19%), coronary arteries (9%), and superior mesenteric artery (8%). The overall mortality rate in COVID-19 patients with arterial thrombosis could be around 20% due to end-organ injury [6].

Case Report

It is a case report of an 81- year lady that developed fever, vomiting, and bone aches for 3 days before being transferred to the fever hospital with gastrointestinal upset, where she was admitted to

normal ward; such patient did not have any co-morbidities. Her blood tests showed lymphopenia, markedly elevated CRP, increased serum Ferritin, and D-dimer elevated > 3 times the normal levels. The diagnosis of COVID-19 was confirmed by RT-PCR, and CT chest revealed peripheral bilateral ground-glass opacity (GGO), however the patient had mild respiratory symptoms.

The patient was managed according to the current protocol of COVID-19, and she improved and discharged to home after one week, but did not continue the anticoagulant medications at home, 5 days later she started to complain of painful right foot then the pain involved the whole leg later on with fixed color changes and coldness. However, the diagnosis of acute ischemia was missed for one week more until the patient came to our department, and arterial duplex revealed extensive thrombosis of the SFA, popliteal and tibial arteries with no detectable arterial blood flow. Such patient developed critical limb ischemia (CLI), and the ABI was<0.4 (Fig.1).

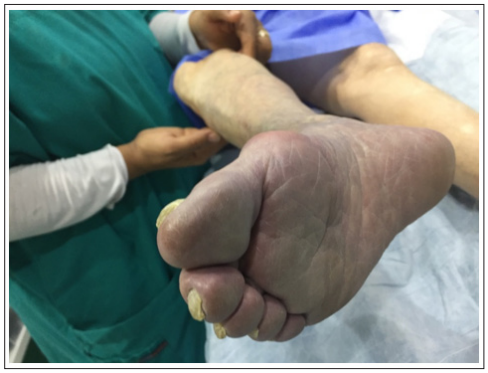

Figure 1: The signs of acute ischemia

The patient was prepared for prompt vascular intervention and surgical embolectomy was performed via combined popliteal and femoral approaches. We started by a medial popliteal approach, however we couldn't at first identify the popliteal artery because it was much collapsed with marked surrounding adhesions. So we decided to do a femoral approach and we used Fogarty catheters 3 and 4 F; a long, thick, more gelatinous and darker thrombus was retrieved both proximally and distally. Then we came back to the popliteal artery again, and with the help of Fogarty catheter introduced via the femoral artery and passing along the popliteal artery working as a stent, and especially after its dilatation, we could explore the artery and complete selective embolectomy distally as well; the artery regained good pulsation with fairly good distal runoff and limb perfusion, however unfortunately completion intraoperative angiogram was not available (Fig.2 A, B) and (Fig.3).

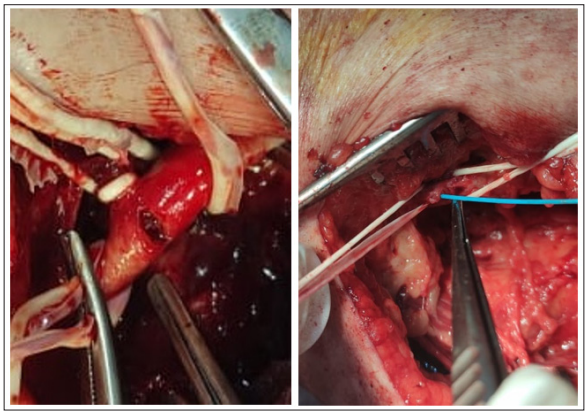

Figure 2: (A) femoral approach (B) medial popliteal approach

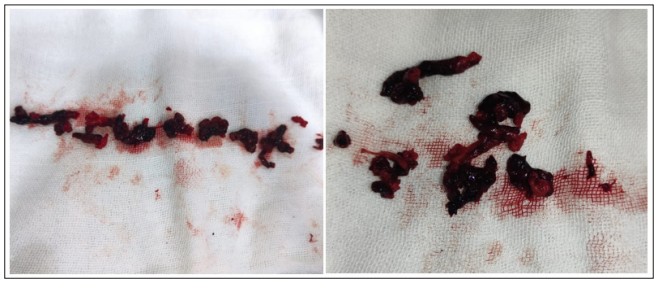

Figure 3: A long, thick, more gelatinous, and darker thrombus

The patient had uneventful postoperative course and kept on Enoxaparin 60 mg/ 12h S/C for one week then shifted to Apixaban 5 mg/12h orally for 3 months, and this was guided by follow- up of D-dimer levels. One week after the operation the patient slipped and developed fracture neck femur of the same limb, and she was operated on one month later. The patient had been followed for 12 months and up till now both clinically and by duplex. The limb was saved, and such lucky 81years lady kept a viable well-functioning limb and could walk again (Fig.4 A, B).

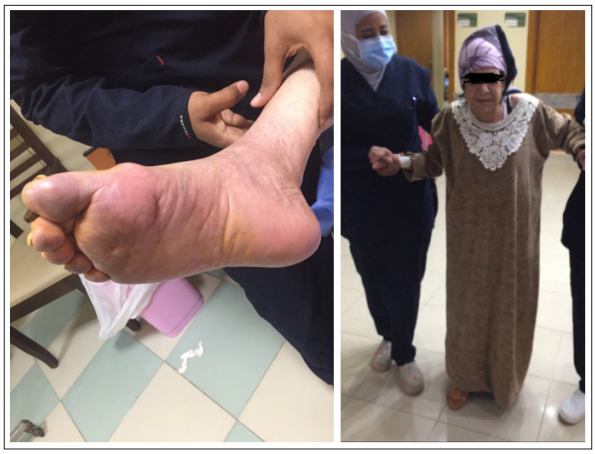

Figure 4: (A) the limb was well perfused (B) the patient could walk again

Discussion

There are limited data with a few scattered reports on arterial thrombosis in COVID-19 infected patients, and emerging evidence suggests that the hypercoagulable state characterized by micro-and macro-vascular thrombotic angiopathy is commonly observed in severe forms of coronavirus disease, however in our case study the patient presenting with major limb arterial thrombosis had a mild form of the disease with mainly gastrointestinal symptoms and did not have any co-morbidities, even did not need ICU admission. So we need further research work to investigate the underlying mechanism of arterial thrombosis that can happen even in mild cases of COVID-19 infection and do work-up to exclude genetic predisposition and arterial thrombogenicity in such patients. Our patient is an 81- year old and elderly age is considered as a risk factor due to age- associated increase in the plasma concentration of coagulation factors such as fibrinogen, factors V, VII, VIII, and X, as well as the von Willebrand′s factor, as already established by many studies [7, 8].

There is a substantial pool of evidence that COVID-19 is associated with endotheliitis and hypercoagulability, along with prolonged immobilization of critically ill COVID-19 patients, thus completing Virchow′s triad and explaining the mechanism of arterial thrombosis. Endotheliitis can result from direct viral infection

which is facilitated by the abundant expression of angiotensin-converting enzyme receptor 2 (ACE2), the receptor for cell entry of SARS-CoV-2, in endothelial cells (ECs). There is a histological evidence of diffuse endothelial damage and inflammatory cells infiltration, and vascular inflammation with endothelial dysfunction is an established precursor to the pathogenesis of arterial thrombosis [9-11]. As regards, the hypercoagulable state, this hypothesis is evidenced by the significant elevation of D-dimer (> 6 times the upper limit), prothrombin, and fibrinogen levels reducing clot formation time and increasing clot firmness, and this could explain the characteristic features of COVID-19 related thrombus which looks like long, thick, more gelatinous and darker thrombus as found in our case report [12,13].

Furthermore, systemic hyper inflammation and cytokines storm observed in severe COVID-19 infection, and laboratory confirmed by elevated pro-inflammatory cytokines, including tumor necrosis factor, interleukin [IL]-6, and IL-1B, monocyte chemoattractant protein-1 (MCP-1) and interferon γ, activate the coagulation cascade. Tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor, is commonly used in management of critically-ill COVID-19 patients [14,15]. Complement (C) has emerged as a potential key contributor to the development of inflammation and tissue damage in COVID-19 patients, with the release of the pro-inflammatory peptides C3a and C5a that help to recruit leukocytes to the lung and other infected tissues and the assembly of the terminal complex that damage vascular endothelium and promotes thrombus formation [16]. The thrombotic microangiopathy(TMA) associated with COVID-19, sometimes be generalized, appears to be more a complement-mediated thrombotic microangiopathy (via the lectin pathway), rather than that due to sepsis-induced coagulopathy or disseminated intravascular coagulation(DIC). There are clinical trials of using complement inhibitors (eculizumab and ravulizumab, both binding to C5) to inhibit downstream complement activation [17].

In conclusion, evidence based data of arterial thrombosis in COVID-19 is still scarce; therefore, we need further investigation to improve our therapeutic targets. The key points of our case study include vigilant consideration of the arterial thrombosis in COVID-19 infected patients, even in the absence of venous thrombosis, routine monitoring of D-dimer levels with initiation of full-dose anticoagulation if levels elevated by six times the upper limit of normal, as well as prompt diagnosis of ALI, and urgent surgical revascularization to save the limb and life of our patients.

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Ethical Statement
The study protocol was approved by the Local Medical Ethics Committee. Informed consent was obtained from all individual participants in the study.

Declaration of Competing Interest
No benefits have been received from a commercial party related directly or indirectly to the subject of this manuscript.

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