Print ISSN: 2321-6379
Online ISSN: 2321-595X

Case Series

Disability Due to Thromboembolism in Covid Recovered Patient

Pancy Sonia Moses[1], Sachin Verma[2], Priyanka Bamoriya[3], Sarvagya Jain[4], Prakhar Chaudhary[4], Chetan Chauhan[4]

[1]Professor, Department of Surgery, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh, India, [2]Associate Professor, Department of Surgery, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh, India, [3]Senior Resident, Department of Surgery, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh, India, [4]Post Graduate Student, Department of Surgery, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh, India

Abstract

Peripheral arterial disease is mainly caused by atherosclerosis and thromboembolic disease. In coronavirus disease (COVID) era, we found there was an exponential increase in the cases of lower limb gangrene due to thrombus in the lower limb arterial system, resulting in the amputation. As COVID infection is hypercoagulable state this results in the thrombus. We want to report a case series of eight patients presented in M.G.M. Medical College and Maharaja Yashwant Rao Hospital, Indore. In all the following patients, on palpation, there was absent Dorsalis Pedal artery pulsation. For the routine imaging, Color Doppler and computed tomography angiography were done for the detection of the level of occlusion/cougulopathy. Hence, the only option left was amputation. The D-dimer has been shown to be frequently elevated in patients with COVID-19. Increased fibrinogen, fibrin degradation products, prothrombin time, activated partial thromboplastin time, and shortened thrombin time have been described in patients with COVID-19 compared to healthy controls. Clinicians are using prophylactic, intermediate, or therapeutic doses of anticoagulation, based on coagulation parameters and the clinical scenario. Although the optimal dosing remains unclear the benefit of anticoagulation with heparin products (mostly low-molecular-weight heparin at prophylactic doses) in COVID-19 patients.

Key words: Amputation, Anticoagulant, Coronavirus disease, Gangrene, Thromboembolism

INTRODUCTION

Peripheral arterial disease is mainly caused by atherosclerosis and thromboembolic disease. In coronavirus disease (COVID) era, we found there was an exponential increase in the cases of lower limb gangrene due to thrombus in the lower limb arterial system, resulting in amputation. As COVID infection is hypercoagulable state this results in thrombus. We want to report a case series of eight patients presented in M.G.M. Medical College and Maharaja Yashwant Rao Hospital, Indore. In all the following patients, on palpation, there was absent Dorsalis Pedal artry pulsation.

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www.ijss-sn.com

Month of Submission : 07-2021
Month of Peer Review : 08-2021
Month of Acceptance : 08-2021
Month of Publishing : 09-2021

Objective

The objective of the study is to present a series of cases with peripheral vessel thrombosis related to COVID-19. Unpredictable clinical presentation is emerging as a hallmark of severe acute respiratory syndrome coronavirus 2 (SARS-COV-2).

MATERIALS AND METHODS

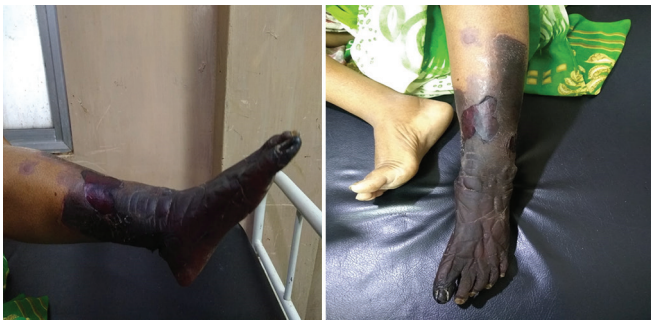
Study was conducted in M.G.M. Medical College and M.Y Hospital, Indore, we, hereby, describing eight patients of the month of June 2021. All eight patients which we had studied were having a history of COVID and positive COVID antibodies. For the routine imaging, we have done Colour Doppler and computed tomography (CT) angiography for the detection of level

Corresponding Author: Dr. Sarvagya Jain, Department of Surgery, Mahatma Gandhi Memorial Medical College, Indore, Madhya Pradesh, India.

of occlusion/cougulopathy. Hence, the only option left was amputation.

CASE REPORT 1

A 65-year-old female, presented with a complaint of left lower limb gangrene for 2 months which was painful, started in the foot and rapidly progressive in nature, and up to mid-calf line of demarcation was present. Colour Doppler was suggestive of proximal poplial artry thrombosis. Finally, above-knee amputation was done.



CASE REPORT 2

A 60-year-old male, presented with complaint of the right lower limb gangrene, with impairment of right foot function, painful for 15 days. Line of demarcation was present at the level of just proximal to the right knee. Colour Doppler was suggestive of Right Superficial Femoral Artery (SFA) complete thrombus with no distal flow seen. At the end, the patient was managed with above-knee amputation.

CASE REPORT 3

A 80-year male, presented with right great toe gangrene for 6–7 days. Colour Doppler was s/o right Distal SFA Occlusion.

CASE REPORT 4

A 55-year male, presented with left great toe gangrene for 2 months. Color Doppler was s/o. left Distal SFA thrombosis.

CASE REPORT 5

A 65-year-male, presented with a chief complaint of pain in the abdomen for 1 month, patient was passing motion and flatus. From the last 5 days patient, I s passing black tarry stool. Contrast-Enhanced CT (CECT) (w+p) was suggestive of thrombus completely occluding aorta and bilateral common iliac vessels distal to the origin of renal arteries.

CASE REPORT 6

Channu More 5o year male presented with complaint of difficulty in walking with a tingling sensation in the right leg for 6 months. CT angiogram was suggestive of complete proximal SMA thrombus and with good distal collaterals. 60–70% Right common iliac thrombus artery occlusion. Right SFA complete thrombus occlusion.

CASE REPORT 7

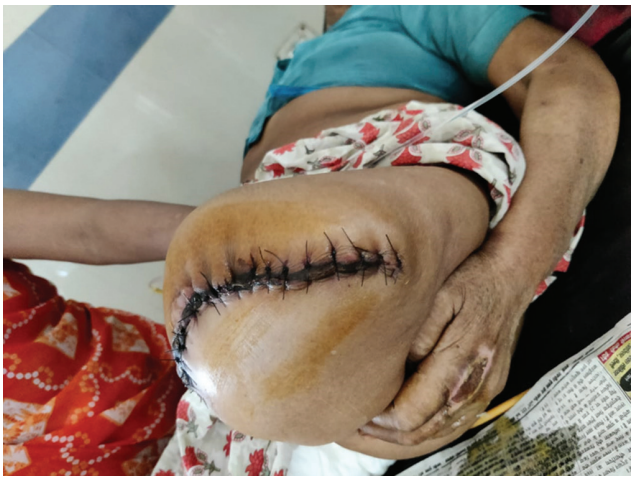
A 90-year–old female patient presented with a complaint of blackening of the left great toe for 45 days, associated with pain.

CASE REPORT 8

A 82-year-old male presented with blaceking of the right lower limb for 1 month and pain for 15 days. Color Doppler s/o thrombus occluding common femoral artery, SFA, deep femoral artery,and right popliteal artery.

CT Images (w/a+p): Thrombus completely occluding aorta and bilateral common iliac vessels distal to the origin of renal arteries.

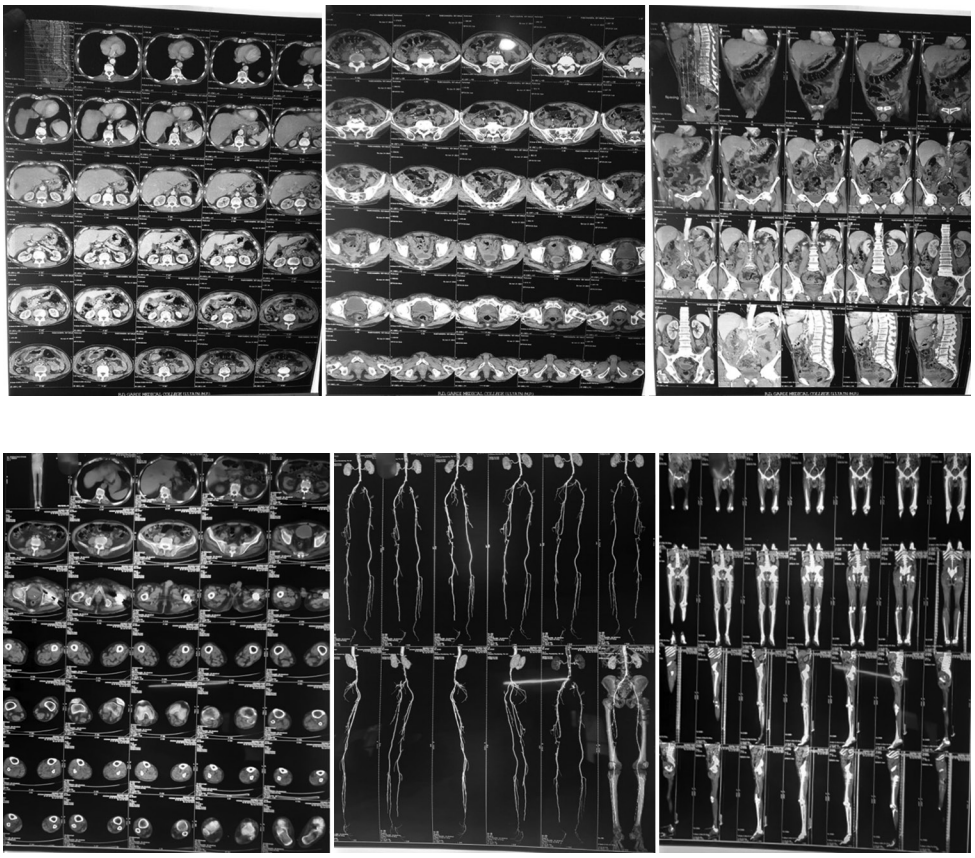
CT Angio S/O Left distal SFA artery thrombus.



Post-Operative Picture

DISCUSSION

COVID pandemic created havoc in the world. From underdeveloped to well-developed countries, each and



every country was severely effect and their were piles of dead bodies. Nobel Coronavirus affected >7 million people worldwide and claimed >400,000 lives as of June 2020.[1,2]

When COVID was started, everyone was thinking that it is mainly a medical disease and there will be no surgical role. However, after few months when the patient recovered from the COVID, they started having painful gangrenous limbs.

Coagulopathy, in the form of arterial and venous thromboembolism, is emerging as one of the most severe sequela of the disease, and has a poorer outcomes.[3-6] Reports of high incidences of thrombosis even after giving prophylactic and therapeutic doses of anticoagulation raise question about a pathophysiology unique to COVID-19.[7,8] Proposed hypotheses include a severe inflammatory response that leads to thrombo-inflammation, through mechanisms such as cytokine storm, complement activation, and endotheliitis.[4,5,9,10] It has also been suggested that the virus itself can activate the coagulation cascade.[11]

Pathophysiology of COVID-19 Coagulopathy: Inflammatory Thrombosis. The relationship between thrombosis and inflammation is well established.[12]

COVID-19 causes a profoundly pro-inflammatory state, as evident from multiple reports of high C-reactive protein, interleukin-6 (IL-6), ferritin, lactate dehydrogenase, and D-dimer levels.[13] fibrinogen and IL-6 levels are shown to relate with each other in COVID patients, providing the idea of inflammatory thrombosis.[14]

Localized Intravascular Coagulopathy

As per studies (Tang *et al.* and CICERI), initial viral damage occurring in the alveoli generates inflammation and local microvascular thrombosis. This is followed by more generalized endothelial dysfunction and thrombo-inflammation in the microvasculature of the kidneys, brain kidneys and other organs leading to a hypercoagulable state and multiple organ failure and finally death.[15-17]

Inflammatory Cytokines

The cytokine profiles in patients with severe COVID-19 show increased production of IL-6, IL-7, TNF alpha, and inflammatory chemokines such as CCL2, CCL3, and soluble IL-2 receptor. Excessive cytokine release contributes to thrombosis through multiple mechanisms, including activation of monocytes, neutrophils, and the endothelium, all of which generate a prothrombotic state and finally thrombus in a vessel causing obstruction.[18-20]

Endothelial Activation and Dysfunction

Endothelial activation or dysfunction with COVID-19 may occur through multiple mechanisms. This includes

inflammatory cytokines generated in the pulmonary interstitium, the activation of the complement components in blood, or possibly, as a direct result of SARS-CoV-2 infection of endothelial cells through the ACE2 receptor.[21] Endotheliitis later causes thrombosis.

Mononuclear Phagocytes

Activated monocytes rapidly upregulate tissue factor expression. This triggers the coagulation cascade resulting in the production of thrombin which, in turn, leads to thrombus generation, platelet activation, and amplification of pro-inflammatory pathways, primarily through PAR signaling.[22]

Complement-mediated Microangiopathy

Researchers in China observed complement hyper-activation in COVID-19 patients, as well as significantly increased plasma C5a levels in severe cases. Dysregulated complement system activation may be a major contributor to cytokine storm, particularly through the pro-inflammatory effects of anaphylatoxins C3a and C5a.[23]

Management

The first general rule in the management of coagulopathy is the treatment of the underlying cause. However, with COVID-19, treatments of the viral infection remain experimental at the current time. As such, until an effective treatment option is available, it is crucial to be able to appropriately manage the sequela of COVID-19-associated coagulopathy.

Monitoring of Laboratory Parameters

As a result of the crosstalk between inflammatory and thrombotic pathways, infections are almost always associated with a concomitant activation of the coagulation system, evidenced by elevation in the markers of an activated coagulation system. The D-dimer has been shown to be frequently elevated in patients with COVID-19. Increased fibrinogen, fibrin degradation products, prothrombin time, activated partial thromboplastin time, and shortened thrombin time have been described in patients with COVID-19 compared to healthy controls.

Anticoagulation

Use of prophylactic or therapeutic dose anticoagulants

As our understanding of the coagulopathy associated with COVID-19 evolves, the best approach to management continues to be explored. Given the paucity of data in the pathophysiology of this disorder, physicians globally are compelled to prepare guidelines for the management of this hypercoagulable state based on the established understanding of crosstalk between inflammation and thrombosis. Thus, clinicians are using prophylactic, intermediate, or therapeutic doses of anticoagulation, based on coagulation parameters and the clinical scenario. Although the optimal dosing remains unclear the benefit of anticoagulation with heparin products (mostly low-molecular-weight heparin [LMWH] at prophylactic doses) in COVID-19 patients was demonstrated by a study in China.[24]

Drug Interactions with anticoagulants and antiplatelets

The effect of direct oral anticoagulants appears to be potentiated by atazanavir, lopinavir/ritonavir, hydroxychloroquine and decreased by tocilizumab. Furthermore, apixaban may confer increased risk for QT prolongation when used with hydroxychloroquine. Atazanavir and lopinavir/ritonavir may decrease the active metabolite of clopidogrel and prasugrel. Among atazanavir, lopinavir/ritonavir, remdesivir, hydroxychloroquine, tocilizumab, and interferon beta, there has not been shown to be interactions with heparin products, fondaparinux, or argatroban.[25]

Duration of anticoagulation

The International Medical Prevention Registry on Venous Thromboembolism (IMPROVE) venous thromboembolic event (VTE) risk score has been used as a tool to identify patients who would benefit from extended-use prophylaxis with LMWH.[26] Protocols suggest that patients hospitalized with COVID-19, especially those with an IMPROVE VTE score of >3, an elevated D-dimer level (>2× upper limit of normal), and 2 or more of the following characteristics: age >60, previous VTE, known thrombophilia, current cancer, should be strongly considered for extended thromboprophylaxis up to 39–45 days post-discharge either with prophylactic dose LMWH or rivaroxaban.[26-28] For patients who have been empirically started on therapeutic anticoagulation for suspected PE, the ASH panel recommends that they should remain anticoagulated for at least 3 months, regardless of results of future investigation studies. Furthermore, cases of confirmed VTE should be considered as "provoked" and treated for 3–6 months duration.[29]

Antifibrinolytics

The use of anti-fibrinolytics is not yet a strong recommendation due to major complications of bleeding. An alternative, safer approach that may confer benefit in COVID-19 induced acute respiratory distress syndrome (ARDS) is the use of nebulized fibrinolytics. In 2019, a study on 60 patients with ARDS showed that use of nebulized streptokinase in patients with severe ARDS resulted in improvements in oxygenation and lung mechanics more rapidly than nebulized heparin.[30] Another agent with fibrinolytic properties that has been considered is Nafamostat. Nafamostat is a synthetic serine protease inhibitor that has been used in Japan for the treatment of DIC in pancreatitis for decades. Nafamostat possesses both anti-fibrinolytic activities as well as anti-viral activity and has

thus generated interested in being repurposed as a potential therapeutic agent for COVID-19 in ongoing studies.[31]

Hence with the proper use of anticoagulant, we can prevent the gangrene of a limb and hence the amputation.

CONCLUSION

COVID-19 is a major risk factor of peripheral thromboembotic state that may endanger patient's life and may lead to amputation Despite therapeutic anticongoagulants, still all COVID-19 patients are at risk for thromboembolic phenomenon, high index of suspicion should be created and with minimal symptoms surgical consultation should be obtained as soon as possible.

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How to cite this article: Moses PS, Verma S, Bamoriya P, Jain S, Chaudhary P, Chauhan C. Thromboembolism in Post Coronavirus Disease Recovered Patient. Int J Sci Stud 2021;9(6):9-13.

Source of Support: Nil, **Conflicts of Interest:** None declared.