ISSN: 2754-4761

Journal of Pulmonology Research & Reports

SCIENTIFIC Research and Community

Case report

Open Access

Peripheral Vascular Complications in COVID-19: Bilateral and Multiple Extensive Thrombophlebitis of the Lower Limbs

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ABSTRACT

Background: COVID-19 infection is now a serious global pandemic (declared by WHO on 11 March 2020), inflicting significant morbidity and mortality, and the rapidly increasing numbers of the infected cases constitutes a burden on the health care system and the economy even in the developed countries. The objective of this case study is to highlight the peripheral vas-cular complications of COVID-19 as the published articles regarding this subject are scarce.

Methods: It is a case report of a 41 year female patient that developed laboratory confirmed (RT-PCR) COVID-19 infection of moderate severity that needed hospitalization for 3 weeks with no need to ICU, and the patient was discharged after improvement. One month later she had peripheral vascular complications in the form of bilateral and multiple extensive thrombophlebitis of her lower limbs. Unfortunately, there was one more month lag before reaching to proper diagnosis and management and the patient was not anticoagulated during all this period since the onset of her COVID-19 infection. She was properly managed on an outpatient basis by LMWH then one of the DOACs together with Aspirin and the patient is being followed for 3 months up till now with excellent results.

Conclusion: COVID-19 can cause hypercoagulability state, resulting in venous thromboembolism and pulmonary embolism with fatal outcome so that all patients with severe COVID-19 infection should be routinely anticoagulated. We should also be aware of the peripheral vascular complications of COVID-19 either venous or arterial not to be missed in diagnosis and should be properly managed.

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Received: August 28, 2020; **Accepted:** September 04, 2020, **Published:** September 10, 2020

Keywords: Covid-19; Vascular; Thrombophlebitis; Anticoagulants; Complement.

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). SARS-CoV and the Middle East Respiratory Syndrome (MERS)-CoV are two previous epidemics caused by Coronavirus. COVID-19 infection is now a serious global pandemic (declared by WHO on 11 March 2020), inflicting significant morbidity and mortality, and the rapidly increasing numbers of the infected cases constitutes a burden on the health care system and the economy even in the developed countries [1].

Our knowledge of COVID-19 is still evolving; however a considerable amount of evidence based data recently showed that the disease is not just pulmonary involvement but significantly affect other systems especially cardiovascular (CV) system that may develop late in the course of more severe cases resulting in bad prognosis. Several cardiovascular syndromes due to COVID-19 have been reported including myocardial damage, arrhythmia, and acute coronary syndrome [2].

There is much focusing on the cardiovascular rather than the peripheral vascular complications either venous or arterial, and the published articles regarding such complications are scarce, so that in our case study we highlight the venous form of peripheral vascular complications of COVID-19 in the form of bilateral and multiple extensive thrombophlebitis of the lower limbs.

Approximately 81% of infected patients have mild disease, whereas, severe disease develops in 14% of patients; pneumonia with ARDS is the most common severe manifestation. Critical illness with septic shock and multiorgan dysfunction has been reported in 5% of COVID-19 patients [3].

Patients and Methods

It is a case report of 41 year female patient that developed high fever, fatigue with bone aches and myalgia, dry cough, anorexia, and characteristically anosmia and dysgeusia, but she did not have any comorbidities. During such epidemic, COVID-19 is suspected and the patient was isolated at home; however she had acute respiratory distress and transferred to hospital where she was admitted and had been investigated. COVID-19 infection was laboratory confirmed by real time RT-PCR; other laboratory findings were increased CRP, lymphopenia, and increased LDH. The pulmonary CT showed peripheral bilateral ground glass opacity (GGO).

The patient was managed according to the protocol currently used which included Hydroxychloroquine, Oseltamivir, Azithromycin,

Zinc and vitamin C supplements; but no anticoagulants were given, just Aspirin as blood thinner. The patient improved on treatment and discharged to home after 3 weeks isolation. One week later she started to complain of her both lower limbs in the form of warmth, tenderness, pain, redness, and swelling affecting multiple scattered areas of both limbs anteriorly and posteriorly. The patient asked for medical help, but unfortunately wasted one month without real diagnosis and management; then she came to us as outpatient consultation, and by patient examination, the clinical diagnosis of bilateral multiple thrombophlebitis was evident and confirmed by Duplex ultra sound that showed no DVT, competent SFJ and SPJ on both sides, incompetent perforators, and multiple superficial varicosities having thrombophlebitis, related to both GSV and Small saphenous veins on both sides; moreover segments of the Great and Small saphenous veins themselves were affected by the thrombophlebitis. The laboratory findings showed high CRP, ESR, S. Ferritin, but D-dimer was normal, and RT-PCR for COVID-19 was negative. The patient was managed on outpatient basis according to her request, and we gave her LMWH (Enoxaparin sodium 80 mg S/C every 12hours) for one week together with Aspirin 81 mg and pain killers, and she improved a lot, then we shifted her to one of DO-ACs (Rivaroxaban 15 mg twice daily for one week then 20 mg at night once) for 3 months. Also, we recommended compression stockings to prevent further complications of varicose veins.

Results

Our case report was a 41-year female patient that did not have any co morbidities, and she developed laboratory confirmed (RT-PCR) COVID-19 infection of moderate severity that needed hospitalization for 3 weeks with no need to ICU, and the patient was discharged after improvement. Then one month from the onset of the clinical manifestations of infection she had peripheral vascular complications in the form of bilateral and multiple extensive thrombophlebitis of her lower limbs on top of superficial varicosities; however, unfortunately this condition was undiagnosed for one month more, and the patient was not anticoagulated during all this time. Duplex –confirmed diagnosis of such very rare condition was made and the patient was successfully managed starting by LMWH then DOACs together with Aspirin, and the patient is being followed for 3 months up till now.

Discussion

The virus binds and enters the cell through angiotensin converting enzyme 2(ACE2) which is present in the lung, heart, intestinal epithelium, vascular endothelium, and the kidney, that is why this novel virus targets these organs specifically. COVID-19 can result in systemic inflammation, multiorgan dysfunction, and critical illness up to death [4].

One study reported that the incidence of confirmed venous thromboembolism(VTE) is 27% and arterial thrombotic events is 3.7% following COVID-19 infection; however PE was the most frequent thrombotic complication. The diagnosis of VTE and PE in COVID patients is challenging; elevated D-dimer levels are not specific to the diagnosis of VTE; however D-dimer greater than 6 times the upper limit is considered significantly important. COVID-19 can cause hypercoagulability state; infection induced dysfunction of the endothelial cells can result in excess thrombin generation and fibrinolysis shutdown. Increasing blood viscosity secondary to hypoxia in severe COVID-19 cases can also be a contributing factor in stimulating thrombosis. A transcription factor dependent signaling pathway in duced by hypoxia also plays a role in increasing the blood coagulability. Prophylaxis with LMWH is recommended for every patient, if not contraindicated, and this regimen is found to be associated with lower mortality in patients having severe COVID-19 with markedly elevated D-dimer. Direct acting oral anticoagulants (DOACs) can also be used in treatment of VTE in COVID-19 infection, but taking into consideration the possible drug interactions with the antiviral medications, as well as dosing adjustment in patients with impaired kidney function [5].

Another study reviewed the thrombotic microangiopathy(TMA) associated with COVID-19, sometimes be generalized, showing the TMA 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). The hematologic and vascular complications seen in severely affected patients often result in serious and fatal out comes with coronavirus infection especially in presence of comorbidities such as diabetes, hypertension, obesity, CV diseases, so that many centres routinely anticoagulate hospitalized (but not ambulatory) COVID-19 patients. Thus, it appears vasculopathy, possibly complement and/or autoantibody mediated, may be one of several final damage pathways in severe COVID-19 patients. Currently anticoagulation is standard in such patients, while we are looking for the clinical trial results utilizing complement inhibitors (eculizumab and ravulizumab, both binding to C5) to inhibit downstream complement activation [6].

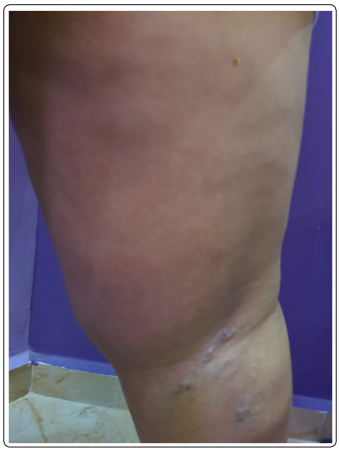

Figure 1: extensive thrombophlebitis of the right GSV

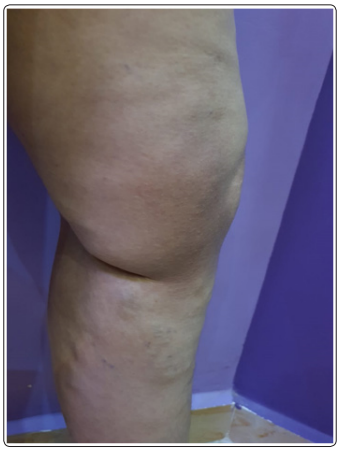

Figure 2: thrombophlebitis related to left GSV

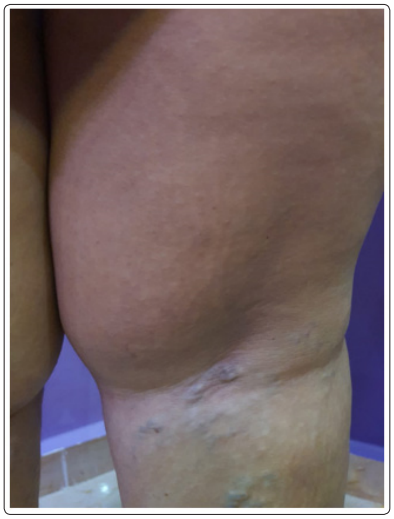

Figure 3: extensive thrombophlebitis of the right lower limb

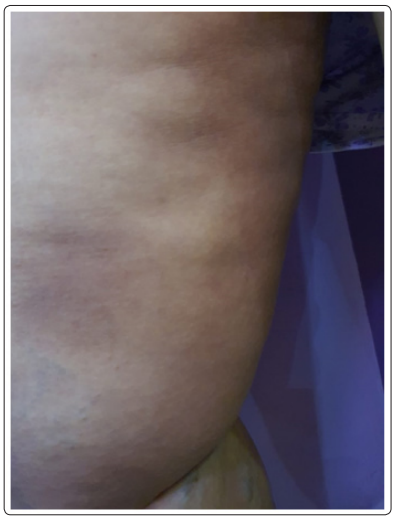

Figure 4: Thrombophlebitis of the right GSV at the thigh

Figure 5: Thrombophlebitis related to GSV distally in both legs

Conclusion

COVID-19 can cause hypercoagulability state, resulting in venous thromboembolism and pulmonary embolism with fatal outcome so that all patients with severe COVID-19 infection should be routinely anticoagulated and according to many studies this can be continued up to 3 months from the onset of the infection as such serious complications can occur late as happened in our case study. We should also be aware of the peripheral vascular complications of COVID-19 either venous or arterial not to be missed in diagnosis and should be properly managed.

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