IJHS

Case Report

SARS-CoV-2 gamma variant and chronic arterial insufficiency due to late arterial thrombosis

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WEBSITE: ijhs.org.sa
ISSN: 1658-3639
PUBLISHER: Qassim University

ABSTRACT

The current evidence suggests a state of hypercoagulability as one of the sequelae of hyperinflammation. Thus, it is an important pathogenic mechanism that contributes to increase the mortality caused by COVID-19. The aim of the present study is to report chronic arterial insufficiency after post-thrombosis in the same arteries 32 days later, as a sequel after severe acute respiratory syndrome coronavirus 2 P.1. After the 2nd day of discharge, she had a lot of pain in her left and limiting leg and was referred to the vascular service. The patient was evaluated by vascular surgery who underwent a clinical diagnosis of Rutherford II.A arterial thrombosis and underwent arteriography of the limb that revealed thrombosis of the anterior, posterior, and fibular arteries in the middle third and the plantar arch was not contrasted. She underwent emergency embolectomy with selective isolation of the tibial arteries, but with success after the procedure only for the posterior tibial artery. Anticoagulation was maintained and 100 mg aspirin was associated.

Keywords: Arterial, COVID-19, thrombosis

Introduction

Among the multiple complex pathophysiological mechanisms underlying COVID-19 pneumonia, immunothrombosis has been shown to play a key role.[1] Viral infection into lung, muscular, and endothelial cells results in inflammatory response including edema, degeneration, and necrotic alterations.[2] The clinical evolution of post-COVID-19 patients who had arterial thrombotic events should be monitored for possible sequelae that may occur.[3]

The current evidence suggests a state of hypercoagulability as one of the sequelae of hyperinflammation. Thus, it is an important pathogenic mechanism that contributes to increase the mortality caused by COVID-19. This hypothesis is supported by reports of elevated inflammatory and clotting markers and a correlation between elevated levels of interleukin (IL)-6 and fibrinogen.[4] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for initiating severe inflammatory responses that can lead to macrovascular and microvascular thrombosis.[5] However, it is not known how long the inflammation and thrombotic disorders can last after recovery from SARS-CoV-2 symptoms.

Antithrombotic prophylaxis involves drugs that interfere with platelet aggregation and the coagulation cascade. Low-dose aspirin may reduce the risk of admission to the intensive care unit and mechanical ventilation in patients hospitalized with SARS-CoV-2,[6] but anticoagulation is one of the main approaches associated with reduced mortality.[7] Despite the widespread use of thromboprophylaxis, patients hospitalized with SARS-CoV-2 rare at increased risk of arterial ischemia and subsequent loss of limbs or even death.[8]

Genome sequencing of viruses sampled in Manaus between November 2020 and January 2021 revealed the emergence and circulation of a worrying new variant of SARS-CoV-2. The Gamma variant strain acquired 17 mutations, including a trio in the spike protein (K417T, E484K, and N501Y) associated with increased binding to the human ACE2 receptor (angiotensin-converting enzyme 2).[9]

Recent review study reported the same observations, where generalized systemic inflammation and procoagulable/hypercoagulable state in COVID-19, including thrombotic microangiopathy, endothelial dysfunction, bleeding disorder, and thrombosis.[10] A retrospective study in the United States, COVID-19 reports an increased risk of venous thrombosis within 90 days, but not arterial thrombosis, compared to influenza.[11] One of the current problems relates to the COVID-19 adenoviral vaccines that have been shown to trigger TTS; however, reports of patients who received COVID-19 mRNA vaccines are also present.[12] Arterial thrombosis and its sequelae have been little reported, as well as the measures to be taken. The aim of the present study is to report chronic

arterial insufficiency after post-thrombosis in the same arteries 32 days later, as a sequel after SARS-CoV-2 Gamma variant.

Case Report

We report the case of a female, 42-year-old patient who had SARS-CoV-2 Gamma variant who was hospitalized. An angiotomography of the chest was requested, which revealed 50% pulmonary impairment used oxygen and but was not intubated. After the 2nd day of discharge, she had a lot of pain in her left and limiting leg and was referred to the vascular service 3 days after the onset of pain. The patient was evaluated by vascular surgery who underwent a clinical diagnosis of Rutherford II. A arterial thrombosis and underwent arteriography of the limb that revealed thrombosis of the anterior, posterior, and fibular arteries in the middle third and the plantar arch was not contrasted. She underwent emergency embolectomy with selective isolation of the tibial arteries, but with success after the procedure only for the posterior tibial artery. She was hospitalized for 13 days, using conventional heparin, then enoxaparin and marevan until she was in a therapeutic range with INR from 2 to 3.

She received the guidelines and was suggested to walk and keep life close to normal. After 17 days of discharge, she presented a new episode of pain in her leg during the walk, for about 100 ms and returned to the vascular surgery service. Absence of anterior and posterior tibial pulses was detected, the systolic pressure was 60 mmHg anterior tibial and 70 mmHg in the left leg with an ankle arm index of 0.61.

An ecodoppler was performed that revealed patency of the iliac, femoral, popliteal arteries, but the tibioperonary trunk was not seen. The anterior tibial artery occluded at the origin, however with refilling by collaterals in the middle third; the posterior tibial artery with monophasic flow in the proximal and middle segment, however with distal occlusion. The fibular artery occluded proximal and middle segment and patent distal segment.

Anticoagulation was maintained and 100 mg aspirin was associated. The diagnosis was chronic arterial insufficiency after 32 days of late arterial thrombosis after the first SARS-CoV-2 Gamma variant thrombosis. She is currently 6 months without a new thrombotic event and with an improvement in her lameness to 400 m. Warfarin was discontinued and only aspirin was maintained.

Discussion

The present study is the first case described in the literature of post-SARS-CoV-2 Gamma variant arterial retrombosis, 32 days after the first episode that progressed to chronic arterial insufficiency in a patient with full anticoagulation with marevan. We currently have ten cases of arterial thrombosis due to SARS-CoV-2 P.1, but this is the first case with rethrombosis and as a consequence of chronic arterial insufficiency.

COVID-19 is an infectious disease whose main cause of morbidity and mortality is vascular disease, mainly of thrombotic or embolic origin. Regarding the treatment of an infection, the elimination or neutralization of the causal agent should be the main objective. However, in relation to SARS-CoV-2 Gamma variant, this option has not been emphasized; therefore, it remains to prevent complications and sequelae.

The main complication is the vascular one causing the thrombotic and embolic event where the use of drugs that interferes with platelet aggregation and the coagulation cascade has been used. Aspirin has alleviated the severity of the case by reducing its worsening in some patients. An coagulants in the prophylactic or therapeutic form of thrombosis are one of the main options; however, they must be analyzed for each case of using the prophylactic or intermediate dosage.

However, the biggest challenge is regarding the emphasis of immunothrombosis and which has the inflammatory aspect as a factor. However, the big question is how to treat and prevent it in the acute and chronic phase. In the acute phase, conducts differ in relation to what we do in non-COVID patients. We had three options up to that point, amputation for patients who arrived late at the vascular center and the limb was already necrotic. Another option was to perform a minor therapeutic procedure, which was embolecatomy instead of bypass or vascular procedure. Moreover, the third option was full anti-cogulation in patients with viable limbs and the possibility of keeping viable with treatment.

The hypothesis for both thrombotic events is the acute endothelial injury caused by inflammatory processes. In the first episode, the treatment with conventional heparin allowed the endothelium to recover and kept the arteries patent for more than 30 days. In the second episode, the hypothesis of an inflammatory process of the musculature of the vessel initially, without involving the endothelium initially, and with the evolution of the inflammation affected the endothelium causing the second thrombotic event.

We detected that there was a failure in the prophylaxis of thrombotic events in patients with Covid 19, mainly in intensive care units. Other options in this prophylaxis, such as the association of aspirin, for prophylaxis of the thrombotic event are suggested. The different viral variants had different behavior in relation to the thrombotic event and all these aspects must be analyzed.[9,13] The greatest recurrence of thrombosis in the highest titers of antibodies anticardiolipin is another alert factor regarding its presence and the need for chronic anticoagulation.[13]

This patient was treated at the second largest teaching hospital in the country, where about 7000 patients have already been

admitted to the intensive care units and wards COVID-19, but the number of venous thrombotic events was significantly higher compared to the atrial ones. However, the evolution of these patients suggests that routine post-COVID-19 prophylaxis is not suggested, as we did initially. Only the most severe cases with a history of peripheral, pulmonary, or visceral thrombotic involvement. This patient was anti-coagulated for 6 months and now only using aspirin and started to limp for 400 meters.

Embolectomy, fibrinolysis, and heparinization are the main approaches taken in these patients and in the literature, there are several case reports of arterial thrombosis, where the conducts were similar.[14-17]

Conclusion

Immunothrombosis is the new hypothesis of vascular surgeons to justify atypical chronic thrombotic events in post-SARS-CoV-2 Gamma variant. Embolectomy is a therapeutic option for these patients and the use of fibrinolysis only for selected cases. Heparinization is the important clinical option in cases, where the limb is not at risk of pear and major vascular sequelae.

Authors' Declaration Statements

Patient's consent statement and approval ethical committee

The study was approved Ethical Committee Faculdade de Medicina de São Jose do Rio Preto-Brazil number# 4.712.867 and the patient signed consente form.

Data availability statement

The data used to support the findings of this study are included within the article.

Competing interests

The authors declared no have conflicts interest.

Funding statement

The authors declared no have financial support

Authors' Contribution

Design and conduct of the study: Godoy JMP, Marum G, Santos HA, Da Silva MOM, Silva FC; Collection data: Godoy JMP, Marum G, Santos HA, Da Silva MOM, Silva FC; Management: Godoy JMP, Marum G, Santos HA, Da Silva MOM, Silva FC. Analysis and interpretation of the data: Godoy JMP, Marum G, Santos HA, Da Silva MOM, Silva FC; Preparation: Godoy JMP, Marum G, Santos HA, Da Silva MOM, Silva FC; Review: Godoy JMP, Marum G, Santos HA, Da Silva MOM, Silva FC All authors approved this manuscript.

References

1. de Godoy JM, Russeff GJ, Cunha CH, Sato DY, Silva DF, Godoy HJ, *et al*. Increased prevalence of deep vein thrombosis and mortality in patients with COVID-19 at a referral center in Brazil. Phlebology 2022;37:21-5.
2. Azer SA. Covid-19: Pathophysiology, diagnosis, complications and investigational therapeutics. New Microbes New Infect 2020;37:100738.
3. de Godoy JM, Russeff GJ, Santos HA, de Godoy AC. Stenosis of large lower limb arteries in a teenager after COVID-19 infection. Med Sci 2021;25:2680-4.
4. Bösmüller H, Traxler S, Bitzer M, Häberle H, Raiser W, Nann D, *et al*. The evolution of pulmonary pathology in fatal COVID-19 disease: An autopsy study with clinical correlation. Virchows Arch 2020;477:349-57.
5. Borrelli MP, Buora A, Scrivere P, Sponza M, Frigatti P. Arterial thrombotic sequalae after Covid-19: Mind the gap. Ann Vasc Surg 2021;75:128-35.
6. Ahmed HA, Merrell E, Ismail M, Joudeh AI, Riley JB, Shawkat A, *et al*. Rationales and uncertainties for aspirin use in COVID-19: A narrative review. Fam Med Community Health 2021;9:e000741.
7. Moll M, Zon RL, Sylvester KW, Rimsans J, Chen EC, Ghosh AJ, *et al*. Intermediate versus standard dose heparin prophylaxis in COVID-19 ICU patients: A propensity score-matched analysis. Thromb Res 2021;203:57-60.
8. Opcu AC, Ozturk-Altunyurt G, Akman D, Batirel A, Demirhan R. Acute limb ischemia in hospitalized COVID-19 patients. Ann Vasc Surg 2021;74:88-94.
9. Hamulyák EN, Scheres LJ, Marijnen MC, Goddijn M, Middeldorp S. Aspirin or heparin or both for improving pregnancy outcomes in women with persistent antiphospholipid antibodies and recurrent pregnancy loss. Cochrane Database Syst Rev 2020;5:CD012852.
10. Acharya Y, Alameer A, Calpin G, Alkhattab M, Sultan S. A comprehensive review of vascular complications in COVID-19. J Thromb Thrombolysis 2021;53:586-93.
11. Ward A, Sarraju A, Lee D, Bhasin K, Gad S, Beetel R, *et al*. COVID-19 is associated with higher risk of venous thrombosis, but not arterial thrombosis, compared with influenza: Insights from a large US cohort. PLoS One 2022;17:e0261786.
12. Hafeez MU, Ikram M, Shafiq Z, Sarfraz A, Sarfraz Z, Jaiswal V, *et al*. COVID-19 vaccine-associated thrombosis with thrombocytopenia syndrome (TTS): A systematic review and post hoc analysis. Clin Appl Thromb Hemost 2021;27:10760296211048815.
13. de Godoy JM, de Godoy MF, Braile DM. Recurrent thrombosis in patients with deep vein thrombosis and/or venous thromboembolism associated with anticardiolipin antibodies. Angiology 2006;57:79-83.
14. da Silva MO, Amorim Santos H, da Silva AF, Marum G, de Godoy JM. Thrombosis of the right iliac, femoral, popliteal, and tibial arteries in a post-COVID-19 in adolescent. Ann Pediatr Surg 2021;17:57.
15. Santosa YP, Yuwono A. Two different clinical presentations of acute limb ischemia caused by acute thrombotic events in COVID-19. Cureus 2021;13:e17916.
16. Faries CM, Rao A, Ilonzo N, Hwong S, Krishnan P, Farhan S, *et al*. Follow-up after acute thrombotic events following COVID-19 infection. J Vasc Surg 2022;75:408-15.e1.
17. Teng E, Pignanelli M, Hammad F, Wisa D. A COVID-19 patient with recurrent acute limb ischaemia despite two successive types of therapeutic dose anticoagulation and thrombolysis. BMJ Case Rep 2021;14:e245040.