Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Vascular Nursing 40 (2022) 69–71

Contents lists available at ScienceDirect

Journal of Vascular Nursing

journal homepage: www.sciencedirect.com/journal/journal-of-vascular-nursing

Review of Case Study: Chowdhry, Moshman, and Caroll (2021). A Case of COVID-19 Related Coagulopathy Complications and Heparin Resistance

Rebecca JL Brown, PhD, MEd, RN

VA Quality Scholar, Minneapolis VA Healthcare System, One Veterans Drive, Building 9, Minneapolis, MN 55417

Introduction

Our understanding of the effects of COVID-19 infection continues to evolve two years into the pandemic. COVID-19 associated coagulopathy is one of many complications documented and may occur in infected patients irrespective of disease severity, in the active or recovery phase of disease, and in the young as well as old.[1–3] A combination of inflammation, coagulation disruption, and endothelial dysfunction have been implicated in micro and macrovascular thromboses throughout the vasculature resulting in heavy and diffuse clot burden.[4]

Venous and arterial thrombotic complications were first identified by Klok et al. in critically ill patients and have been well documented since as notable manifestations of COVID-19.[1,4,5] Non-critically ill patients with COVID-19 have also been found to have COVID-19 associated coagulopathies as well as patients who have recovered from COVID-19.[2,3]

This clinical column highlights a case report recently published in *Cureus Journal of Medical Science*.[3] The authors document the course of COVID-19 associated coagulopathy progression in a 33-year-old male who had recovered from mild COVID-19 infection. For the comprehensive case details, please see Chowdrhry, Moshman, and Carroll's publication.[3]

Article Summary

Presentation to the Emergency Department

A 33-year-old male with undiagnosed diabetes (hemoglobin A1C 12%) and obesity presented to the emergency department (ED) with severe and acute onset pain and swelling in his left leg and foot, loss of motor function of the ankle and foot, and numbness. Assessment showed his left leg was cool with mottling of the skin, diminished sensation, monophasic popliteal pulse on the left side, bilateral palpable femoral, dorsalis pedis and posterior tibial pulses, foot drop, inability to flex the ankle, minimal ability to flex or extend the toes, pain with dorsiflexion of the foot and a palpable cord of the left lower extremity. The patient reported progressively worsening pain and noted that the motor impairment began five days prior to his arrival in the ED.

Ultrasound Findings and Initial Operating Room Visit

The patient underwent an ultrasound of the left lower extremity revealing new nearly occlusive deep venous thromboses in the popliteal and gastrocnemius veins as well as nearly occlusive thromboses in the femoral, posterior tibial, anterior tibial, and peroneal arteries. He was started on a heparin infusion immediately. Vascular surgery performed an open thrombectomy of the superficial femoral artery (SFA), popliteal, anterior tibial (AT), posterior tibial (PT), and peroneal arteries under general anesthesia. Heparin was titrated per protocol and at therapeutic levels, however the patient had recurrent thromboses. The popliteal artery was occluded again within a few minutes of surgical closing as well as the tibial vessels requiring immediate reintervention. After the reintervention, the patient's oxygen saturation dropped to the low 70s% while on 100% fraction of inspired oxygen (FiO2) and he became tachycardic and was therefore intubated. Dorsalis pedis pulses were obtainable, however the posterior tibial artery reoccluded a third time and reintervention was not an option given the patient's worsening respiratory condition.

Post-operative Period

He remained in tachycardia and respiratory function worsened. An electrocardiogram showed a ST segment elevation myocardial infarction in the inferior leads with reciprocal anterior ST depression and thus he was sent to the cardiac catheterization lab and found to have triple vessel disease. Percutaneous coronary intervention was unsuccessful. The patient went into a-flutter and was cardioverted with amiodarone. Echocardiogram confirmed multiple thrombi in his heart. During this period, the anterior tibial artery reoccluded and he was unable to return to the OR for a third thrombectomy. That patient underwent guillotine amputation of

E-mail address: Rebecca.Brown4@va.gov

https://doi.org/10.1016/j.jvn.2022.02.003
1062-0303/Published by Elsevier Inc. on behalf of Society for Vascular Nursing, Inc.

the left foot including the ankle. Additional thrombectomies of the posterior and anterior tibial arteries were performed with restoration of flow thereafter.

Following the STEMI and amputation of the patient's left foot, he developed pulseless ventricular tachycardiac and was resuscitated. He managed to be extubated and was improving for one week before his first of two episodes of acute hypoxemic respiratory failure requiring re-intubation and mechanical ventilation. Ultimately, during the peri-intubation period, the patient showed pulseless electrical activity and resuscitation was attempted. The patient underwent 30 minutes of advanced cardiac life support. A cardiac ultrasound showed a ventricular thrombus. The patient was pronounced dead.

Heparin Resistance During Course of Care

Heparin was administered throughout the initial vascular procedure of the SFA, popliteal, AT, PT, and peroneal arteries per protocol. During this procedure, activated clotting time (ACT) was therapeutic between 250-300. Despite achieving a therapeutic ACT, the patient still had multiple thrombi throughout his body. In the postoperative period, the patient remained on a heparin infusion titrated per standard protocol, however the patient could no longer reach the therapeutic range with an activated partial thromboplastin time (aPTT) of 55.7 seconds, suggesting heparin resistance. Thus, an alternative anticoagulant (Argatroban) was started and reached therapeutic levels within 24 hours (aPTT 114.8 seconds). The patient was bridged with fondaparinux to warfarin following the STEMI. Despite this management, the patient still died due to hypercoagulation, despite being only 33 years old. Extensive workups were conducted to determine the source of the hypercoagulability with all negative results, suggesting COVID-19 associated coagulopathy.

Reviewer Comments

Post recovery complications in young individuals are important to recognize and triage appropriately. Patients infected with COVID-19 without prior history of vascular disease may present with initial symptoms of peripheral artery disease (PAD), acute ischemic stroke, or venous thromboembolism without any respiratory symptoms.[6,7] Goldman et al. reported amputation rates of 38% in patients who tested positive for COVID-19 compared to 3% in COVID-19 negative patients and a 25% mortality rate compared to 3% in COVID-19 negative patients.[8] This case is one of many documented cases of profuse venous and arterial thromboembolism, despite coagulation.[4] Notable laboratory exams include elevated d-dimer, thrombocytopenia, and specific tests to determine dynamic measures of clot strength and speed such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM).[4]

Nursing Implications

Early recognition of symptoms and appreciation of the unique characteristics of COVID-19 associated coagulopathy compared to non-COVID-19 presentations are critical components of providing care, even in young patients and even following recovery post COVID-19 infection.

The inflammatory response caused by the virus is a suspected major contributing factor to the hypercoagulable state seen in many patients with COVID-19.[4] This is likely exacerbated by immobility potentially related to increased sedentary behavior during recovery and/or isolation. It is still unclear whether increased physical activity or exercise may be an effective ancillary therapy to reduce incidence of COVID-19 associated coagulopathy.

Regarding prophylactic anticoagulation, previously, it has not been uniformly recommended given the high risk of bleeding,[9-11] however, a recent randomized controlled trial (the "ACTION" trial - Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration) determined that prophylactic anticoagulation, chiefly with heparin, was superior to therapeutic anticoagulation with oral anticoagulants. Furthermore, therapeutic anticoagulation with oral anticoagulants was associated with increased bleeding.[12] Heparin may have increased benefit due to its anti-inflammatory effects and possible antiviral effects.[13] Therefore, it remains unclear how to proceed when patients experience heparin resistance.

Given the potential for prolonged coagulopathies, considerations in timing of elective surgeries should be carefully evaluated and patients should be included in shared decision making when possible. The United Kingdom guidelines for timing of elective surgery state patients should be at least seven weeks post infection in those with transient or asymptomatic disease and longer for those with more severe disease and those who have been hospitalized.[14] The COVIDSurg Collaborative, an international, cohort study including data from 235 hospitals in 24 countries, measured 30-day postoperative mortality and pulmonary complications in patients who had COVID-19 infection within 7 days before surgery or 30 days after surgery and found half of patients have postoperative pulmonary complications and 30-day mortality was 23.8%.[15]

Further investigation is needed to determine the long-term vascular impact of COVID-19 infection. Currently, there appears to be no published literature on coagulopathies related to COVID-19 associated coagulopathy with Delta or Omicron variants. As COVID-19 continues to evolve, so will our understanding of the long-term effects of COVID-19 disease and vascular complications related to new variants.

Declaration of Competing Interest

The author declares that there is no conflict of interest.

Funding Acknowledgements

This publication was made possible by funding to Dr. Brown from the VA Quality Scholars program. The content is solely the responsibility of the author and does not necessarily represent the views of the funding agency.

References

1. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145–147. doi:10.1016/j.thromres.2020.04.013.
2. Trimaille A, Curtiaud A, Marchandot B, et al. Venous thromboembolism in non-critically ill patients with COVID-19 infection. *Thromb Res*. 2020;193:166–169. doi:10.1016/j.thromres.2020.07.033.
3. Chowdhry E, Moshman J, Carroll S. A Case of COVID-19 Related Coagulopathy Complications and Heparin Resistance. *Cureus*. 2021;13(9):e18265 Published 2021 Sep 25. doi:10.7759/cureus.18265.
4. Goswami J, MacArthur TA, Sridharan M, et al. A Review of Pathophysiology, Clinical Features, and Management Options of COVID-19 Associated Coagulopathy. *Shock*. 2021;55(6):700–716. doi:10.1097/SHK.0000000000001680.
5. Hippensteel JA, Burnham EL, Jolley SE. Prevalence of venous thromboembolism in critically ill patients with COVID-19. *Br J Haematol*. 2020;190(3):e134–e137. doi:10.1111/bjh.16908.
6. Oxley TJ, Mocco J, Majidi S, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med*. 2020;382(20):e60. doi:10.1056/NEJMc2009787.
7. Ilonzo N, Rao A, Berger K, et al. Acute thrombotic events as initial presentation of patients with COVID-19 infection. *J Vasc Surg Cases Innov Tech*. 2020;6(3):381–383. doi:10.1016/j.jvscit.2020.05.011.
8. Goldman IA, Ye K, Scheinfeld MH. Lower-extremity Arterial Thrombosis Associated with COVID-19 Is Characterized by Greater Thrombus Burden and Increased Rate of Amputation and Death. *Radiology*. 2020;297(2):E263–E269. doi:10.1148/radiol.2020202348.

9. Thachil Jecko, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *Journal of Thrombosis and Haemostasis*. 2020;18(5):1023–1026.
10. Langer Florian, et al. Coagulopathy in COVID-19 and its implication for safe and efficacious thromboprophylaxis. *Hämostaseologie*. 2020;40(3):264–269.
11. Moores Lisa K, et al. Prevention, diagnosis and treatment of venous thromboembolism in patients with COVID-19: CHEST Guideline and Expert Panel Report. *Chest*. 2020;158(3):1143–1163.
12. Lopes RD, de Barros E, Silva PGM, Furtado RHM, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. *Lancet*. 2021;397(10291):2253–2263. doi:10.1016/S0140-6736(21)01203-4.
13. Hippensteel JA, LaRiviere WB, Colbert JF, Langouët-Astrié CJ, Schmidt EP. Heparin as a therapy for COVID-19: current evidence and future possibilities. *Am J Physiol Lung Cell Mol Physiol*. 2020;319:L211–L217.
14. El-Boghdadly K, et al. SARS-CoV-2 infection, COVID-19 and timing of elective surgery: a multidisciplinary consensus statement on behalf of the Association of Anaesthetists, the Centre for Peri-operative Care, the Federation of Surgical Specialty Associations, the Royal College of Anaesthetists and the Royal College of Surgeons of England. *Anaesthesia*. 2021;76(7):940–946.
15. COVIDSurg CollaborativeMortality and pulmonary complications in patients undergoing surgery with perioperative SARS-CoV-2 infection: an international cohort study. *Lancet*. 2020;396:27–38.