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.

Annals of Vascular Surgery - Brief Reports and Innovations 2 (2022) 100101

Contents lists available at ScienceDirect

Annals of Vascular Surgery - Brief Reports and Innovations

journal homepage: www.elsevier.com/locate/avsurg

Covid-19 Delta variant resulting in multi system thromboembolic disease

Gabriella Fluss[a,*], Victoria Cranwell[b], Ajit Rao[c], Joon Sub Lee[d], Ramy Elshafey[e], Marc Wallack[f], David Finlay[g,*]

[a] Department of Surgery, New York Medical College at Metropolitan Hospital Center, New York, NY, USA
[b] Department of Surgery, New York Medical College at Metropolitan Hospital Center, New York, NY, USA
[c] Department of Vascular Surgery, Icahn School of Medicine, Mount Sinai Medical Center, New York, NY, USA
[d] School of Medicine, New York Medical College, Valhalla, NY, USA
[e] Department of Surgery, New York Medical College at Metropolitan Hospital Center, New York, NY, USA
[f] Associate Professor Surgery and Radiology, Icahn School of Medicine at Mount Sinai Medical Center, NY, USA
[g] Division Chief Vascular Surgery, New York Medical College at Metropolitan Hospital Center, NY, USA

ARTICLE INFO

Keywords:
Covid-19
Thrombosis
Thromboembolism
Delta
Unvaccinated

ABSTRACT

Infection with severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2/Covid-19) has been correlated with micro and macrovascular thrombosis. Reports have discussed localized thrombosis leading to ischemia, we report a case of diffuse systemic thromboembolism resulting in limb ischemia and organ damage from Covid-19 despite prompt anticoagulation. A 60-year-old unvaccinated male with a history of asthma, diabetes mellitus and coronary artery disease, presented with shortness of breath and right lower extremity pain. The patient was found to be Covid-19 Delta variant positive. CTA and transthoracic echocardiogram showed diffuse thromboembolic disease affecting the left ventricle, right kidney and bilateral lower extremities.

Introduction

The presentation of Covid-19 varies and has a wide spectrum of symptoms, most commonly affecting the upper respiratory system. But, since its emergence there has been a continuous increase in the reports of coagulopathies resulting from the virus, with recent case reports demonstrating both micro and macrovascular thromboembolisms. Coagulation disorders related to Covid-19 are triggered by hyperactive and dysregulated coagulation through a wide array of interconnected immunological pathways. The current understanding of the pathophysiology is that endothelial dysfunction and increased platelet activation triggered by the virus leads to a hypercoagulable state.[1] The Delta variant has been shown to be more contagious, and cause more severe symptoms than the previous variants. Although the exact pathophysiology is still being studied, molecular analysis has shown the spike protein of the virus' Delta variant to have increased affinity for the endothelium.[2] It has already been established that vascular endothelial cells play an important role in inflammation and coagulation. Endothelial cells respond to cytokines released by leukocytes by expressing cell adhesion molecules and growth factors, promoting inflammatory response and coagulation. With disruption of the endothelial barrier, the coagulation cascade is activated and patients exhibit a hypercoagulable state which may lead to thrombo-embolic events.[18]

There are many reports documenting deep vein thrombosis and/or pulmonary embolism from Covid-19, however there are fewer reports on arterial thrombosis and diffuse systemic thromboembolism resulting in systemic organ damage despite proper anticoagulation.[3,4] We present a case of a patient who presented with localized arterial thrombosis, which then progressed to diffuse disease affecting the heart, kidney, and bilateral lower extremities.

Case report

A 60-year-old unvaccinated male with a history of asthma, uncontrolled diabetes mellitus and two prior cardiac stents (not on antiplatelet due to non-compliance), presented to the emergency department (ED) complaining of a two week history of flu-like symptoms and right knee pain. Patient stated that he fell while in the bathroom due to fatigue, crawled back to his bed where he was later awoken at 13:00 by extreme right knee pain. When the patient presented to the ED at 18:00, he complained of worsening right lower extremity (RLE) pain and numbness. On examination his RLE was cold and mottled with no sensory or motor function extending to the thigh. CT angiogram was performed which showed thromboembolic occlusion in the upper pole of right kidney (Fig. 1), right superior and inferior gluteal arteries, right common femoral artery, bilateral profunda arteries (Fig. 2), left internal

* Corresponding authors.
E-mail addresses: Gfluss1@gmail.com (G. Fluss), finlaymd@gmail.com (D. Finlay).

https://doi.org/10.1016/j.avsurg.2022.100101
Received 10 March 2022; Received in revised form 13 June 2022; Accepted 15 June 2022

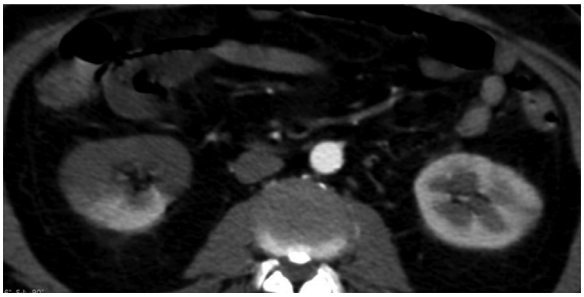

Fig. 1. Thromboembolic disease in the upper pole of right kidney.

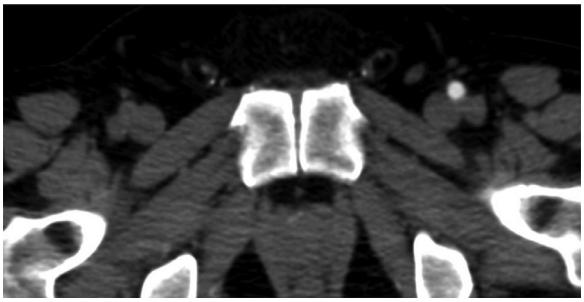

Fig. 2. R SFA and bilateral profunda thrombosis.

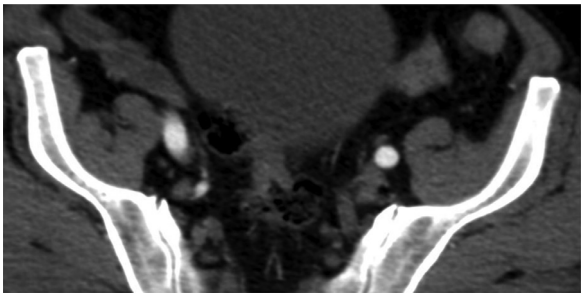

Fig. 3. Thrombosis of the left internal iliac artery.

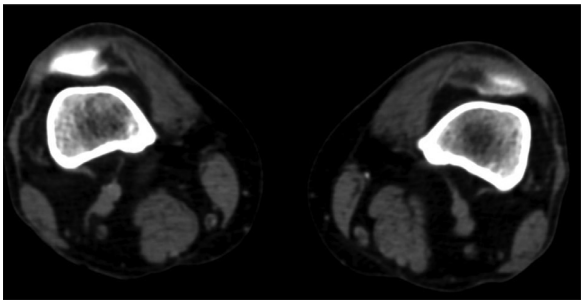

Fig. 4. Bilateral popliteal thrombosis with no runoff.

iliac artery (Fig. 3) and bilateral popliteal arteries (Fig. 4) with no reconstitution on the right and only proximal anterior tibial reconstitution on the left, without runoff to the foot. In addition to diffuse thromboembolic disease with critical limb ischemia, further testing showed that the patient was in diabetic ketoacidosis and had Covid pneumonia resulting from the Delta variant of Covid 19. The patient was given therapeutic Lovenox in the ED, but on admission to the ICU, was started on a therapeutic heparin drip and aspirin 325 mg. He also required BiPAP to maintain oxygen saturation above 90%.

On admission, the patient presented as a Rutherford III, with an ischemic time greater than eight hours, above knee amputation of the RLE was recommended, but in the setting of covid pneumonia and worsening respiratory status it was recommended to first stabilize the patient. Despite full anticoagulation, the patient's thromboembolic disease rapidly progressed, with loss of bilateral femoral dopplerable signals on day two. He remained in sinus rhythm, but a transthoracic echo showed a large multilobular thrombus present in the left ventricle, mildly dilated left artery and ventricle, concentric left ventricular hypertrophy and an EF (ejection fraction) of 20%.

Over the next four days the patient continued to decline. He refused any intervention and asked to be made DNR. His-labs continued trending upward: CPK (796 → 6953 U/L), LDH (883 → 1926 U/L) and D-dimer (57,725 → > 69,000 ng/mL) indicating progression of thrombosis and ischemia of bilateral lower extremities. The vascular surgery team recommended an anti-Xa level be drawn, but this was never done by the ICU. The patient's respiratory status also continued to worsen, in the setting of an EF of 20% the patient developed pulmonary edema leading to hypoxemic respiratory failure secondary to Delta variant pneumonia. He ultimately succumbed to his illness on the 6th day of admission.

The patient had no personal or family history of claudication, transient ischemic attack, stroke, heart attack, clotting or bleeding disorders. He had no prior amputations or evidence of peripheral vascular disease. It is also unknown if the patient had baseline diabetic nephropathy, given that the patient had no labs prior to admission and had not seen a doctor in several years. Most importantly, the patient never received his covid vaccine.

Discussion

Since the emergence of SARS-CoV-2 (Covid-19) in late 2019, there has been increasing evidence in the literature highlighting the thrombogenic effects of the virus. The pathophysiology of Covid-19-induced thromboembolic disease is incredibly complex and has many contributing factors. In brief, the coagulopathies are triggered by hyperactive and dysregulated coagulation through a wide array of interconnected immunological pathways. Infection with Covid-19 results in a significant increase in proinflammatory cytokines due to a hyperactive inflammatory state and a decrease in the regulation of the inflammatory response.[5] The interaction between proinflammatory cytokines, immune cells, and complement components leads to the activation of platelets and formation of clots. Proinflammatory cytokines also induce the expression of tissue factor from endothelial cells, the primary initiator of the extrinsic coagulation cascade, which strongly contributes to a hypercoagulable state.[6] SARS-CoV2 can directly infect endothelial cells inducing apoptosis and endothelial inflammation. These changes trigger the recruitment of macrophages and granulocytes synthesizing proinflammatory cytokines. If the infection is not controlled, the inflammation progresses leading to a procoagulant state, characterized by massive thrombin production.[20]

As a result of Covid-19 infection, platelets become hyperactive and the endothelium is impaired. This is due to their expression of angiotensin-converting enzyme-2 (ACE-2) receptors, which have been identified as the target receptor of the spike protein of Covid-19.[7] ACE-2 receptors are expressed on both platelets and endothelium, which is found in various tissues including the lungs, kidney, heart and blood vessels.[8] The Delta variant has been shown to be more contagious, and cause more severe symptoms than the previous variants. This is the result of the Delta variant having a higher affinity for the ACE-2 receptors on endothelium,[2] which plays a crucial role in the regulation of fibrinolysis and platelet aggregation.[9]

Covid-19 infiltrates these cells by binding to ACE-2 receptors. This action potentiates an intense immune response known as the cytokine storm, which triggers the onset of systemic inflammatory response syndrome (SIRS). The subsequent SIRS can induce an endotheliopathy and hypercoagulability state, leading to both systemic macro and microvascular disease.[10] The heightened inflammatory response, endothelial dysfunction, and increased platelet activation disrupts the balance between

the pro and anticoagulant pathways, resulting in a hypercoagulable state in patients with Covid-19.[1]

The presence of fibrin-rich microthrombi in the pulmonary capillary on autopsy series shows overwhelming evidence of small vessel thrombosis as the main cause of hypoxia.[21] Most patients who encounter thromboembolic complications experience deep vein thrombosis and/or pulmonary embolism. Yet there is constantly increasing evidence in the literature regarding arterial thrombosis[11] and multi system thromboembolic disease. Previous cases present limb and/or digit ischemia.[12,13,14] There are fewer documented cases of thromboembolic disease spreading to the heart and/or brain,[15] and even fewer identifying end-organ infarction in the bowel and/or kidney.[16]

The current report presents a case of COVID-19 Delta variant infection resulting in systemic thromboembolization, limb ischemia, and organ damage. His-presentation of systemic thromboembolic disease, affecting a plethora of vessels, including the profunda femoris (a vessel with minimal documented of occlusion[17]), has not previously been reported. The patient had no significant past medical history or family history of coagulopathies, yet developed diffuse progressive thrombosis despite prompt anticoagulation. It is unknown whether his initial knee injury was a contributing factor, but his prior medical history was significant for two prior coronary stents. However, it is unknown if these stents remained patent or had already occluded from chronic disease. It is possible that an acute occlusion of the stents could have occurred, which was supported by an increased troponin and the presence of a large thrombus found on echocardiogram. Whether this was related to a large embolic event or the sequela of an ongoing thrombosis cannot be known. Lastly, there is currently no proof in the literature that thromboembolic disease can be prevented by the vaccine. However, there are several studies that suggest a strong relationship between the Covid-19 Delta Variant and thromboembolic disease.[19]

The patient described was not a candidate for COVID-related therapies including plasmapheresis, administration of plasma, or therapeutic phlebotomy. These modalities have been shown to reduce hyperviscosity, improve tissue perfusion and oxygenation, and reduce thrombotic complications.[22] Upon surveying the literature, many authors suggest that patients with COVID at high risk for thrombotic complications be given anticoagulant prophylaxis with LMWH or unfractionated heparin (provided they are not at increased risk of hemorrhage), along with anti-viral treatment. There is scant data regarding proper timing/dosage/administration scheme of anticoagulation therapy in Covid-19 patients.[23]

Conclusion

Our case presents a patient with diffuse, rapidly progressing systemic thromboembolization after contracting COVID-19. This case adds to the existing literature documenting the detritus effects of COVID-19 and the new variants, as well as, the need for improved thromboprophylaxis guidelines. This patient never receive a COVID-19 vaccine, and experienced diffuse arterial thromboembolization despite anticoagulation therapy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Vajari MK, Shirin M, Pourbagheri-Sigaroodi A, Akbari ME, Abolghasemi H, Bashash D. COVID-19-related coagulopathy: a review of pathophysiology and pharmaceutical management. *Cell Biol Int*. 2021;45(9):1832–1850. doi:10.1002/cbin.11623.
2. Aleem A, Akbar Samad AB, Slenker AK. *StatPearls*. Emerging variants of SARS-CoV-2 and novel therapeutics against Coronavirus (COVID-19). Treasure Island (FL): StatPearls Publishing; July 18, 2021.
3. Vulliamy P, Jacob S, Davenport RA. Acute aorto-iliac and mesenteric arterial thromboses as presenting features of COVID-19. *Br J Haematol*. 2020;189(6):1053–1054. doi:10.1111/bjh.16760.
4. Kaur P, Qaqa F, Ramahi A, Shamoon Y, Singhal M, Shamoon F, et al. Acute upper limb ischemia in a patient with COVID-19 [published online ahead of print, 2020 May 13]. *Hematol Oncol Stem Cell Ther*. 2020 S1658-3876(20)30096-0. doi:10.1016/j.hemonc.2020.05.001.
5. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med*. 2020 Jun 25;58(7):1021–1028 PMID: 32286245. doi:10.1515/cclm-2020-0369.
6. Borrelli MP, Buora A, Scrivere P, Sponza M, Frigatti P. Arterial thrombotic sequalae after Covid-19: mind the gap. *Ann Vasc Surg*. 2021 Aug;75:128–135 Epub 2021 May 1. PMID: 33940162; PMCID: PMC8087612. doi:10.1016/j.avsg.2021.04.009.
7. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020;17(5):259–260. doi:10.1038/s41569-020-0360-5.
8. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*. 2003;426:450–454. doi:10.1038/nature02145.
9. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. *Lancet*. 2020 May 2;395(10234):1417–1418 Epub 2020 Apr 21. PMID: 32325026; PMCID: PMC7172722. doi:10.1016/S0140-6736(20)30937-5.
10. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J Am Coll Cardiol*. 2020 Jun 16;75(23):2950–2973 Epub 2020 Apr 17. PMID: 32311448; PMCID: PMC7164881. doi:10.1016/j.jacc.2020.04.031.
11. Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. *Thromb Res*. 2020;191:9–14. doi:10.1016/j.thromres.2020.04.024.
12. Putko RM, Bedrin MD, Clark DM, Piscoya AS, Dunn JC, Nesti LJ. SARS-CoV-2 and limb ischemia: a systematic review. *J Clin Orthop Trauma*. 2021;12(1):194–199. doi:10.1016/j.jcot.2020.11.018.
13. VO Costa, de Almeida GBC, Nicolini EM, Rodrigues GA, da Costa BMA, Carvalho GH, et al. Acute arterial occlusion of the lower limb as the main clinical manifestation in a patient with Covid-19 - case report. *Int J Surg Case Rep*. 2020;77:454–458 Epub 2020 Nov 11. PMID: 33200062; PMCID: PMC7657076. doi:10.1016/j.ijscr.2020.11.046.
14. Parvez Y, Khan F. Acute bilateral femoral arterial thrombosis in a young adult: a rare association with asymptomatic COVID-19. *Cureus*. 2021 Apr 25;13(4):e14674 PMID: 34055521; PMCID: PMC8148617. doi:10.7759/cureus.14674.
15. Baghal M, Amrutiya V, Govil S, Patel R, Gabelman M, Gaynor B, et al. Multisystem thromboembolism in a COVID-19 patient: a case report. *J Community Hosp Intern Med Perspect*. 2021;11(4):489–495. doi:10.1080/20009666.2021.1933715.
16. O'Shea A, Parakh A, Hedgire S, Lee SI. Multisystem assessment of the imaging manifestations of coagulopathy in hospitalized patients with coronavirus disease (COVID-19). *AJR Am J Roentgenol*. 2021 Apr;216(4):1088–1098 Epub 2021 Feb 3. PMID: 32755217. doi:10.2214/AJR.20.24132.
17. Labropoulos N, Bekelis K, Jr Leon LR. Thrombosis in unusual sites of the lower extremity veins. *J Vasc Surg*. 2008 May;47(5):1022–1027 Epub 2008 Mar 21. PMID: 18358674. doi:10.1016/j.jvs.2007.12.044.
18. Hink Ulrich, et al. Mechanisms underlying endothelial dysfunction in diabetes mellitus. *Circ. Res.*. 2001;88(2). doi:10.1161/01.res.88.2.e14.
19. Wang Tao, et al. Attention should be paid to venous thromboembolism prophylaxis in the management of COVID-19. *The Lancet Haematology*. 2020;7(5). doi:10.1016/s2352-3026(20)30109-5.
20. de Carranza María, et al. Aortic thrombus in patients with severe COVID-19: review of three cases. *J. Thromb. Thrombolysis*. 2021;51(1):237–242.
21. Jadhav Kartik Pandurang, Jariwala Pankaj. Intra-cardiac thrombus in COVID-19 pandemic–case series and review. *Eur J Cardiovasc Med*. 2020;6(I).
22. Wise J. Covid-19 and thrombosis: what do we know about the risks and treatment? BMJ. 2020 May 21;369:m2058. doi:10.1136/bmj.m2058. PMID: 32439704.
23. Srivastava Swati, et al. COVID-19 infection and thrombosis. *Clinica Chimica Acta*. 2020;510:344–346.