

CLINICAL VIGNETTE

Suspected Asymptomatic COVID-19 Infection and Pulmonary Embolism

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Introduction

The range of symptoms and associated end organ damages from SARS-CoV-2 infection continues to broaden as more data appears. One of higher mortality consequence is pulmonary thromboembolic events. Many severely infected hospitalized patients have pulmonary embolism and/or deep vein thrombosis. Prophylaxis and prevention measures have been studied and recommended based on evolving data. However, the data is limited with mild outpatient cases and even rarer in asymptomatic infected patients. Asymptomatic patients may not be aware of their infection yet they are nevertheless at risk for subsequent thromboembolic events for months afterwards. This case illustrates the suspected COVID infection as cause of bilateral pulmonary embolism in a low thromboembolic risk patient.

Case

A 66-year-old Spanish-speaking woman with history of diabetes, hypertension, thrombophlebitis, presents to ER with 1 day of constant midsternal chest pain and palpitations worse with exertion. She has tachypnea but denies actual shortness of breath. For several weeks, she was more fatigued than usual, but has no other symptoms and denies cough, hematemesis, fever, rash, nausea, vomiting, dizziness nor leg swelling. She denies COVID-19 infection although her daughter had covid infection 6 months prior. She does not smoke nor taking any hormone supplement. She had a prior episode of lower extremity thrombophlebitis many years ago attributed to varicose veins. She denies family history of thrombosis and has been very active.

Physical exam was significant for hypoxia with O₂ saturation of 88% on room air, improving to 94% on 4L O₂. BP 140/76, Pulse 129, respiratory rate was 19 breath/min without respiratory distress. Cardiac exam only showed tachycardia, her lungs were clear and there was no lower extremity edema.

Admission labs were significant for Troponin of 1.15; BNP281; D-dimer 1597; normal PT/INR 12.2/1.0, PTT 34.7, normal CBC and SARS-CoV-2 PCR was negative.

EKG showed sinus tachycardia at rate of 129, without ST/T wave changes. Chest x-ray no evidence of acute disease. Lower extremity venous ultrasound was negative for DVT in either leg.

Chest CT angiography revealed extensive bilateral pulmonary emboli including the distal right pulmonary artery and left pulmonary artery as well as multiple lobar pulmonary arteries bilaterally. Thoracic aorta was normal.

Transthoracic echocardiogram showed LVEF of 50-55%. Moderate to severe reduced systolic functions. Moderate to severe TR with estimated RVSP 50 to 55mmHg with moderate pulmonary hypertension.

Patient was admitted to the ICU and started on infusion heparin with improvement of her symptoms and decreased D dimer to 732. Hypercoagulable work up was negative for Factor V Leiden mutation, prothrombin B20210A Mutation, Beta 2 Glycoprotein 1 Antibodies IgG and IgM, Phospholipid Abs IgM/IgG, normal SED rate.

Patient was able to walk without desaturation and no oxygen required on discharge.

Cardiology deemed elevated troponin due to demand ischemia with right heart strain secondary to bilateral pulmonary embolism. She was subsequently discharged home on apixaban 5 mg BID.

At the post hospital follow up visit, COVID-19 antibody testing was positive due to possible exposure 6 months ago.

Post discharge d-dimer decreased from 0.37 => 0.29 => 0.28.

With her negative hypercoagulable testing and positive COVID-19 antibodies, her bilateral PE were presumed by asymptomatic COVID-19 infection within past 6 months. Patient will complete six months of therapeutic anticoagulation with apixaban.

Discussion

Hypercoagulable state is common in patients with COVID-19 infection especially in the ICU. The pathogenesis of the thromboembolic events due to SARS-CoV-2 infection is not fully understood and speculated as a complex interaction between endothelial cells injury, local and systemic inflammatory response, and the deranged coagulation system.¹ SARS-CoV-2 virus causes endothelial injury with direct invasion of the endothelial cells. In addition, the spike protein could activate

the alternative complement pathway.^{2,3} This hypercoagulable state with acute inflammatory changes has been termed thromboinflammation or COVID-19 associated coagulopathy (CAC)⁴ and has associated vascular dysfunction and cytokine storm. The exaggerated inflammatory immune response and thrombotic microangiopathy subsequently result in multiorgan dysfunction and potential death.^{4,5} One study reported 57 % of 44 ICU patients lack clot lysis function, and were referred as “fibrinolysis shutdown” with higher rate of thromboembolic events.⁶ For critically ill patients, immobilization also leads to stasis of blood flow. Increased Factor VIII, fibrinogen, d-dimer and hyperviscosity are found in infected patients.⁷ Other coagulation labs can be variable, including platelet count, PT/PTT, and clotting time, which can be normal or elevated.⁷

Initial symptoms of SARS-CoV-2 infection are mainly respiratory with chronic pulmonary sequela. Forty to fifty percent of asymptomatic patients were found to have subclinical lung abnormalities on CT scans with possible association to the infection.⁸ PE and other thromboembolic events were linked to critically ill patients with COVID-19 and increase morbidity and mortality.⁵ The hypercoagulable state seems to persist beyond hospital discharge even with thromboprophylaxis.^{9,10} The majority of venous thrombosis events occur within six weeks of hospitalization.¹¹ The incidence of thromboembolic events in ambulatory COVID-19 patients is not clear due to lack of data and the insidious development of PE for those without other risk factors for thromboembolic diseases.⁵ There have only been handful of asymptomatic patient have been diagnosed with acute PE requiring hospitalization and subsequently found to have prior COVID-19 infection with positive antibody or current positive test results.^{5,9,12}

Randomized controlled trials in past year have conflicting results regarding the antithrombotic therapy in COVID-19 patients.¹ Pharmacological thromboprophylaxis is not routinely recommended post discharge for ambulatory patients.^{1,13} Full therapeutic dose low molecular weight heparin might improve outcomes in non-critically ill patients admitted to hospital. However, this may not apply to critically ill patients with higher bleeding risk and impaired renal function. Thus thromboprophylaxis with intermediate dose LMWH may be a better alternative.^{1,13} Consideration for patients with increased risks of thrombosis including obesity, should receive full dose anticoagulation.¹⁴ In sicker ambulatory patients with reduced mobility, elevated d-dimers, or elevated inflammatory parameters, LMWH prophylaxis could be consider in absence of bleeding risk.^{1,9} If VTE is established, a treatment period of 3-6 months is recommended.¹² Recommendations may continue to evolve as more studies and results become available.

This patient had no COVID-19 symptoms nor confirmed infection other than remote exposure through family contact 6 months ago. Her hypercoagulable testing was negative. The subsequent positive COVID-19 antibody test led to the association of COVID infection to her bilateral PE. The patient may have been infected without symptoms within the past 3 months thus resulting in elevated IgG level. T cell immunity

has shown to be robust in convalescent individuals with asymptomatic or mild COVID-19.^{12,15} However, this was not checked for this patient. It is important to consider pulmonary embolism as a potential late complication in patient without severe COVID-19 infection. It is prudent to consider possible remote SARS-CoV-2 infection in patients with unexplained VTE and without risk factors. Much is yet to be known about the long-term effect post COVID-19 infections, the reinfection potential and the risk of thromboembolic events. Long term follow-up and screening for recurrent symptoms may be warranted to prevent fatal events.

REFERENCES

1. **Leentjens J, van Haaps TF, Wessels PF, Schutgens REG, Middeldorp S.** COVID-19-associated coagulopathy and antithrombotic agents-lessons after 1 year. *Lancet Haematol.* 2021 Apr 27;S2352-3026(21)00105-8. doi: 10.1016/S2352-3026(21)00105-8. Epub ahead of print. PMID: 33930350; PMCID: PMC8078884.
2. **Lowenstein CJ, Solomon SD.** Severe COVID-19 Is a Microvascular Disease. *Circulation.* 2020 Oct 27;142(17):1609-1611. doi: 10.1161/CIRCULATIONAHA.120.050354. Epub 2020 Sep 2. PMID: 32877231; PMCID: PMC7580651.
3. **Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, Baxter-Stoltzfus A, Laurence J.** Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: A report of five cases. *Transl Res.* 2020 Jun;220:1-13. doi: 10.1016/j.trsl.2020.04.007. Epub 2020 Apr 15. PMID: 32299776; PMCID: PMC7158248.
4. **Connors JM, Levy JH.** Thromboinflammation and the hypercoagulability of COVID-19. *J Thromb Haemost.* 2020 Jul;18(7):1559-1561. doi: 10.1111/jth.14849. Epub 2020 May 26. PMID: 32302453.
5. **Alharthy A, Balhamar A, Faqihi F, Alshaya R, Noor A, Alaklobi F, Memish ZA, Karakitsos D.** Insidious development of pulmonary embolism in asymptomatic patients with COVID-19: Two rare case-reports. *Respir Med Case Rep.* 2020;31:101186. doi: 10.1016/j.rmcr.2020.101186. Epub 2020 Aug 11. PMID: 32834989; PMCID: PMC7418650.
6. **Wright FL, Vogler TO, Moore EE, Moore HB, Wohlaer MV, Urban S, Nydam TL, Moore PK, McIntyre RC Jr.** Fibrinolysis Shutdown Correlation with Thromboembolic Events in Severe COVID-19 Infection. *J Am Coll Surg.* 2020 Aug;231(2):193-203.e1. doi: 10.1016/j.jamcollsurg.2020.05.007. Epub 2020 May 15. PMID: 32422349; PMCID: PMC7227511.
7. **Singhania N, Bansal S, Nimmatooi DP, Ejaz AA, McCullough PA, Singhania G.** Current Overview on Hypercoagulability in COVID-19. *Am J Cardiovasc Drugs.* 2020 Oct;20(5):393-403. doi: 10.1007/s40256-020-00431-z. PMID: 32748336; PMCID: PMC7398761.
8. **Oran DP, Topol EJ.** Prevalence of Asymptomatic SARS-CoV-2 Infection : A Narrative Review. *Ann Intern Med.* 2020 Sep 1;173(5):362-367. doi: 10.7326/M20-3012.

Epub 2020 Jun 3. PMID: 32491919; PMCID: PMC7281624.

9. **Laouan Brem F, Rasras H, El Ouafi N, Bazid Z.** Bilateral Pulmonary Embolism in Patients Recovered From Asymptomatic COVID-19 Infection. *Cureus*. 2021 Mar 12;13(3):e13848. doi: 10.7759/cureus.13848. PMID: 33854858; PMCID: PMC8038649.
10. **Vadukul P, Sharma DS, Vincent P.** Massive pulmonary embolism following recovery from COVID-19 infection: inflammation, thrombosis and the role of extended thromboprophylaxis. *BMJ Case Rep*. 2020 Sep 13;13(9):e238168. doi: 10.1136/bcr-2020-238168. PMID: 32928824; PMCID: PMC7488789.
11. **Spyropoulos AC, Ageno W, Cohen AT, Gibson CM, Goldhaber SZ, Raskob G.** Prevention of Venous Thromboembolism in Hospitalized Medically Ill Patients: A U.S. Perspective. *Thromb Haemost*. 2020 Jun;120(6):924-936. doi: 10.1055/s-0040-1710326. Epub 2020 Jun 3. PMID: 32492724.
12. **Beckman M, Nyrén S, Kistner A.** A case-report of widespread pulmonary embolism in a middle-aged male seven weeks after asymptomatic suspected COVID 19 infection. *Thromb J*. 2020 Aug 28;18:19. doi: 10.1186/s12959-020-00235-w. PMID: 32868974; PMCID: PMC7453687.
13. **Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, Levi M, Samama CM, Thachil J, Giannis D, Douketis JD; Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis.** Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost*. 2020 Aug;18(8):1859-1865. doi: 10.1111/jth.14929. PMID: 32459046; PMCID: PMC7283841.
14. **Susen S, Tacquard CA, Godon A, Mansour A, Garrigue D, Nguyen P, Godier A, Testa S, Levy JH, Albaladejo P, Gruel Y; GIHP and GFHT.** Prevention of thrombotic risk in hospitalized patients with COVID-19 and hemostasis monitoring. *Crit Care*. 2020 Jun 19;24(1):364. doi: 10.1186/s13054-020-03000-7. PMID: 32560658; PMCID: PMC7303590.
15. **Sekine T, Perez-Potti A, Rivera-Ballesteros O, Strålin K, Gorin JB, Olsson A, Llewellyn-Lacey S, Kamal H, Bogdanovic G, Muschiol S, Wullimann DJ, Kammann T, Engård J, Parrot T, Folkesson E; Karolinska COVID-19 Study Group, Rooyackers O, Eriksson LI, Henter JI, Sönnernborg A, Allander T, Albert J, Nielsen M, Klingström J, Gredmark-Russ S, Björkström NK, Sandberg JK, Price DA, Ljunggren HG, Aleman S, Buggert M.** Robust T Cell Immunity in Convalescent Individuals with Asymptomatic or Mild COVID-19. *Cell*. 2020 Oct 1;183(1):158-168.e14. doi: 10.1016/j.cell.2020.08.017. Epub 2020 Aug 14. PMID: 32979941; PMCID: PMC7427556.