Celiac Artery Thrombosis and Splenic Infarctions: A Rare Complication in Unvaccinated COVID-19 Patient

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ABSTRACT

COVID-19 has been highly linked to a hypercoagulable state among affected patients. This case highlights that COVID-19 associated thrombotic incidents are not exclusive to venous circulation and include atypical arterial thrombosis. Here, we report a case of celiac artery thrombus in self-limited outpatient COVID-19 illness as a rare thrombotic complication of COVID-19 infection.

KEYWORDS: celiac artery thrombosis, splenic infarction, COVID-19 hypercoagulability, COVID-19 arterial thrombosis

CASE REPORT

A 76-year-old male nonsmoker with history of hypertension on amlodipine, unvaccinated for COVID-19 due to personal preference, presented to the emergency department with sharp and severe lower abdominal pain of sudden onset two days prior to arrival. The pain was constant, non-radiating, and not relieved by simple analgesics (such as acetaminophen and ibuprofen). He tested positive for COVID-19 two weeks prior to the onset of abdominal pain and reported mild symptoms, including fever (Tmax 102°F), productive cough, and shortness of breath. His lowest home oxygen saturation measurement was 90%. He remained stable and completed quarantine at home until resolution of these symptoms. He had no known family history of blood disorders, blood clots, or cancers.

On presentation, he was nonobese (BMI 24), afebrile and normotensive, saturating 93% on ambient air. He was not distressed. Lung exam demonstrated decreased air entry bilaterally with bibasilar crackles. His abdomen was soft and nondistended with left-sided tenderness to palpation.

Laboratory results are noted in **Table 1**. CT Abdomen/Pelvis with contrast revealed a partially occlusive thrombus in the distal celiac artery extending into common hepatic artery and multifocal ischemic splenic infarcts without perisplenic hematoma (**Figure 1**). Echocardiogram was negative for right heart strain or evidence of thrombus.

He was started on intravenous heparin for therapeutic anticoagulation. On hospital day 2, hematology was consulted due to the atypical site of thrombus formation and warfarin was initiated due to concern for underlying coagulopathy, including antiphospholipid syndrome. However, coagulopathy work-up returned negative except for only a positive phospholipid (Cardiolipin) Ab, IgM, making antiphospholipid syndrome less likely and not meeting the criteria for diagnosis. The patient was then transitioned to and discharged home on apixaban. Coagulopathy work-up results are noted in **Table 2**.

At the one-month follow-up in the hematology clinic, cardiolipin IgM titer had notably trended down to 22.7 MPL.

Table 1. Laboratory Results at time of hospital admission

WBC	9x10(3)/mcL	**Calcium**	8.5 mg/dL
Hemoglobin	15.2 g/dL	**Covid 19 PCR**	Detected
Hematocrit	41.7%	**Total bilirubin**	1.0 mg/dL
Platelet	272x10(3)/mcL	**AST**	36 Intnl Unit/L
Glucose	109	**ALT**	57 Intnl Unit/L
BUN	11 mg/dL	**Alkaline phosphate**	127 Intnl Unit/L
Creatinine	0.73 mg/dL	**Total protein**	7.1 g/dL
Sodium	131 mmol/L	**Lipase**	31 Intnl Unit/L
Potassium	3.6 mmol/L	**Albumin**	3.1 g/dL
Chloride	97 mmol/L	**Lactic acid**	1.3 mmol/L
Carbon Dioxide	23 mmol/L	**Troponin**	< 0.01 ng/mL x3

Figure 1. Yellow arrow points toward the partially occlusive thrombus in the distal celiac artery extending into the common hepatic artery. Red arrow points toward the splenic infarctions.

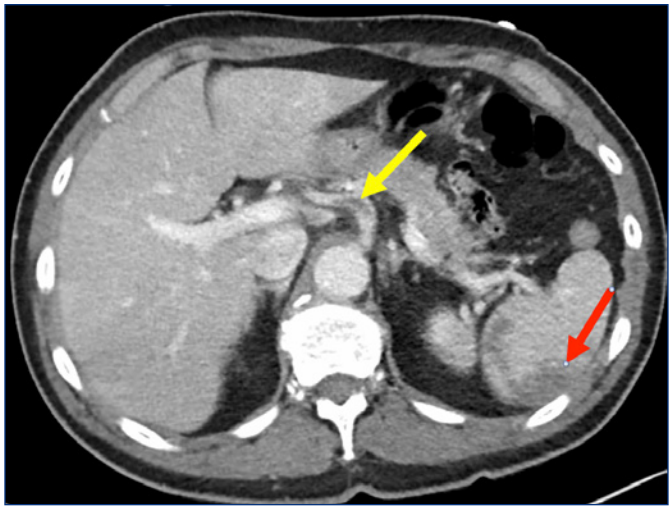

Table 2. Coagulation Work-Up Results

PT	13.8 sec
INR	1.2
PTT	37.2 sec
Protein S Activity	77.9%
Protein S Antigen free	73%
Antithrombin III	72%
Lupus anticoagulation INR	1.2
Activated Partial Thrombopl Time, P	35 sec
DRVVT screen Ratio	1.08
Beta 2 Glycoprotein 1 Antibodies (IgM)	<9.4 U/mL
Beta 2 Glycoprotein 1 Antibodies (IgG)	<9.4 U/mL
Phospholipid (Cardiolipid) Ab, IgG	<9.4 GPL unit
Phospholipid (Cardiolipid) Ab, IgM	74.0 MPL
Factor V Leiden (R506Q) mutation, B	Negative
Paroxysmal Nocturnal Hemoglobinuria	Negative
JAK2 V617F Mutation Detection, Bld	Negative

The decision regarding total duration of anticoagulation was deferred to the next visit in the hematology clinic. A preliminary plan was set for a total of 3-6 months based on the evolving clinical picture of a provoked thrombus in the setting of transient thrombophilia due to COVID-19 infection.

DISCUSSION

Though the high incidence of thrombotic events in COVID-19 patients is increasingly reported in the literature, the underlying mechanism behind this hypercoagulable state remains under investigation. The main mechanisms by which COVID-19 infection intrinsically increases the risk for thromboembolism include 1) systemic inflammation with extensive endothelial dysfunction in both the arterial and venous systems, 2) increased blood viscosity secondary to hypoxemia in severe COVID-19 infection, and 3) abnormal coagulation resulting in acquired thrombophilia due to DIC biology in critical illness.[1] The endothelial damage triggered by severe systemic inflammation increases production of pro-coagulant factors (ie. platelet activating factor and von willebrand factor) with decreased production of the normal anticoagulant factors (protein C, anti-thrombin III) that normally counteract platelet aggregation.

The degree of inflammatory markers' elevation on initial presentation is predictive of coagulation-associated complications among COVID-19 patients, with D-dimer above 2,500ng/mL, platelet count >450x10^9/mcL, CRP>100mg/L, and ESR>40mm/h conferring high risk of thrombosis.[2] The only available parameter from our patient's case to compare to these values is the platelet count, measured to be 272,000/mcL on admission, two weeks after his initial infection.

Antiphospholipid antibodies (aPLs), anti-cardiolipin, anti-β2-glycoprotein, and lupus anticoagulant, emerge after vaccination or infection when self-antigens cross-react with vaccine/viral antigens. Thrombotic events have been reported in recipients of the adenoviral vector or mRNA-based COVID-19 vaccines.[3] aPLs lend endothelial cells a vasoconstricting, pro-thrombotic physiology that promotes coagulation, increases expression of adhesion molecules for leukocytes and platelets, and antagonizes anticoagulant factors.[3-7]

The prevalence of venous thromboembolism in COVID-19 patients reaches up to 30%.[2,4] Overall, arterial thrombosis is less common with an incidence rate of approximately 4% in critically ill patients, the majority of whom are symptomatic with involvement of multiple arteries in approximately 18% of patients.[8,9] The involvement of intra-abdominal vascular arteries is even more rare. Celiac artery thrombosis and splenic infarction are only reported in a few cases.[10,11] Higher frequency of thrombotic events seems to be present more in severely ill patients, in particularly those admitted to intensive care unit.[12] In mild COVID-19 cases, thrombotic events were less common but reported even with absence of lung parenchymal infiltrates, but with lower incidence rate than severely ill patients.[13,14] One explanation for the nondiscriminatory thrombi formation in both arterial and venous circulatory beds is acquired antiphospholipid antibodies seen in COVID-19 and potentially leading to antiphospholipid syndrome that leads to endothelial dysfunction.

Few cases of celiac artery thrombosis and splenic infarction were reported after administration of Oxford vaccine[15] and after ChAdOx1 nCov-19 vaccine (Vaxzevria, AstraZeneca).[16] However, thrombophilia work-up was negative including APLs in these cases.

The clinical utility of aPLs levels in COVID-19 patients is still not well established. Some studies suggest correlation with disease severity and higher incidence of thrombotic events, as patients with multiple aPLs were found to have a significantly higher incidence of cerebral infarction.[6,7] However, despite the prevalence of aPLs in COVID-19 patients, studies suggest low utility for correlating their presence to thrombotic events as they are non-specifically positive in the absence of thrombotic disease and may later test negative as acute illness resolves. In a study of 31 ICU patients, 16 of 22 patients (72%) without thrombosis were aPL positive and 9 of 10 retested aPLs-positive patients were negative on a second test after discharge.[17] This suggests that aPL positivity in COVID-19 patients may not be the sentinel feature predisposing to thrombotic events. In our case, the positive Cardiolipin IgM down-trended at the one-month follow-up, suggesting transient aPL antibody positivity as

most likely an acute phase reactant, rather than marker of true anti-phospholipid disease. Positivity of aPLs during COVID-19 infection is not uncommon and repeat testing at follow-ups is needed before relating these levels to anti-phospholipid disease.

Risk of thromboembolism for COVID-19 patients may persist even after initial presentation. Delayed onset of thrombosis has been reported and seen as late as 4–8 weeks after initial COVID-19 insult.[14,18-21] Unlike venous thrombosis where risk decreases with time since COVID-19 infection, the risk of arterial thrombosis appears to remain stable after infection.[22] The mechanism behind persistent delayed risk of thrombosis in COVID-19 is still not well understood, but presumably attributed to the body's prolonged response to the virus rather than a primary process triggered by the virus itself.

A recent randomized controlled trial included 320 patients comparing post discharge thromboprophylaxis with Rivaroxaban for patients at high risk on discharge (high risk defined as IMPROVE score ≥4 or 2–3 with a D-dimer >500 ng/mL) versus no extended thromboprophylaxis approach on discharge, revealed improved clinical outcomes with less risk of symptomatic or fatal thrombotic events within 35 days (3% risk of thrombotic events in Rivaroxaban group versus 9% in patients with no post discharge thromboprophylaxis).[23] The evidence for post-discharge thromboprophylaxis with antiplatelet therapy, on the other hand, remained lacking with mixed evidence and findings from the current studies.[24-26]

The development of APLs post-COVID-19 vaccination remains one of the theories behind thrombotic events seen after vaccines administration in otherwise healthy individuals. Despite the rare incidence of thrombotic events reported after COVID-19 vaccines, the morbidity and mortality associated with severe COVID-19 infection, including occurrence of thrombotic events, is such that the benefit of COVID-19 vaccination outweighs the risks in order to decrease severity of infection and associated complications.

CONCLUSION

This case of self-limited, non-severe COVID-19 infection with subsequent development of major arterial thrombosis alerts physicians to consider the extent of thrombotic events in patients with even mild COVID-19 infection. Furthermore, thrombotic events are not limited to venous thrombosis and include various sites within the arterial system. However, prophylactic anticoagulation to protect against thromboembolic events in the outpatient settings is still not formally recommended by major society guidelines in the absence of complete randomized control trials.

References

1. Gómez-Mesa JE, Galindo-Coral S, Montes MC, Muñoz Martin AJ. Thrombosis and Coagulopathy in COVID-19. Curr Probl Cardiol. 2021;46(3):100742.
2. Al-Samkari H, Karp Leaf RS, Dzik WH, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020 Jul 23;136(4):489-500.
3. Talotta R, Robertson ES. Antiphospholipid antibodies and risk of post-COVID-19 vaccination thrombophilia: The straw that breaks the camel's back? Cytokine Growth Factor Rev. 2021 Aug;60:52-60.
4. Di Minno A, Ambrosino P, Calcaterra I, et al. COVID-19 and Venous Thromboembolism: A Meta-analysis of Literature Studies. Semin thromb Hemost. 2020 Oct;46(7):763-771.
5. Katneni UK, Alexaki A, Hunt RC, et al. Coagulopathy and Thrombosis as a Result of Severe COVID-19 Infection: A Microvascular Focus. Thromb Haemost. 2020 Dec;120(12):1668-1679.
6. Xiao M, Zhang Y, Zhang S, et al. Antiphospholipid Antibodies in Critically Ill Patients With COVID-19. Arthritis Rheumatol. 2020 Dec;72(12):1998-2004.
7. Hasan Ali O, Bomze D, Risch L, et al. Severe Coronavirus Disease 2019 (COVID-19) is Associated With Elevated Serum Immunoglobulin (Ig) A and Antiphospholipid IgA Antibodies. Clin Infec Dis. 2021 Nov 2;73(9):e2869-e2874.
8. Cheruiyot I, Kipkorir V, Ngure B, Misiani M, Munguti J, Ogeng'o J. Arterial Thrombosis in Coronavirus Disease 2019 Patients: A Rapid Systematic Review. Ann Vasc Surg. 2021 Jan;70:273-281.
9. de Roquetaillade C, Chousterman BG, Tomasoni D, et al. Unusual arterial thrombotic events in COVID-19 patients. Int J Cardiol. 2021 Jan 15;323:281-284.
10. Arslan G. Celiac Artery Thrombosis and Splenic Infarction as a Consequence of Mild COVID-19 Infection: Report of an Unusual Case. Hamostaseologie. 2021 Jul; 1(10):1055/a-1508-7388.
11. Güven C. COVID-19-related Abdominal Aortic Thrombosis. Coll Physicians Surg Pak. 2021 Jul;31(2):S130-S131.
12. Al-Ani F, Chehade S, Lazo-Langner A. Thrombosis risk associated with COVID-19 infection. A scoping review. Thromb Res. 2020 Aug;192:152-160.
13. Manek G, Gupta M, Congrete S, Datta D. Submassive Pulmonary Embolism in Mild COVID-19 Without Lung Infiltrates. Cureus. 2021 Mar 18;13(3):e13978.
14. Vechi HT, Maia LR, Alves MDM. Late acute pulmonary embolism after mild Coronavirus Disease 2019 (COVID-19): a case series. Rev Inst Med Trop Sao Paulo. 2020 Sep 4;62:e63.
15. Bandapaati S, Bobba H, Navinan MR. Coeliac artery and splenic artery thrombosis complicated with splenic infarction 7 days following the first dose of Oxford vaccination, causal relationship or coincidence? BMJ Case Rep. 2021 Jul 14;14(7):e243799.
16. Anderson A, Seddon M, Shahzad K, et al. Post-COVID-19 vaccination occurrence of splenic infarction due to arterial thrombosis. BMJ Case Rep. 2021 Dec 7;14(12):e243846.
17. Devreese KMJ, Linskens EA, Benoit D, et al. Antiphospholipid antibodies in patients with COVID-19: A relevant observation? Thromb Haemost. 2020 Sep;18(9):2191-2201.
18. Karolyi M, Pawelka E, Omid S, Kelani H, Mader T, Baumgartner S, Laferl H, Traugott M, Seitz T, Zoufaly A, Wenisch C. Late onset pulmonary embolism in young male otherwise healthy COVID-19 patients. Eur J Clin Microbiol Infect Dis. 2021 Mar;40(3):633-635.
19. Di Tano G, Moschini L, Loffi M, Testa S, Danzi GB. Late Pulmonary Embolism after COVID-19 Pneumonia despite Adequate Rivaroxaban Treatment. Eur J Case Rep Intern Med. 2020 Jun 18;7(7):001790.
20. 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.

21. Taha M, Nguyen P, Sharma A, Taha M, Samavati L. Forty-One-Year-Old Man with Pulmonary Embolism 5 Months After COVID-19. Clin Med Insights Circ Respir Pulm Med. 2021 Feb 8;15:1179548420986659.
22. Li P, Zhao W, Kaatz S, Latack K, Schultz L, Poisson L. Factors Associated With Risk of Postdischarge Thrombosis in Patients With COVID-19. JAMA Netw Open. 2021 Nov 1;4(11):e2135397.
23. Ramacciotti E, Barile Agati L, Calderaro D, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. Lancet. 2022 Jan 1;399(10319):50-59.
24. Liu Q, Huang N, Li A, et al. Effect of low-dose aspirin on mortality and viral duration of the hospitalized adults with COVID-19. Medicine (Baltimore). 2021 Feb 12;100(6):e24544.
25. Sayed Ahmed HA, Merrell E, Ismail M, et al. Rationales and uncertainties for aspirin use in COVID-19: a narrative review. Fam Med Community Health. 2021 Apr;9(2):e000741.
26. Connors JM, Brooks MM, Sciurba FC, et al. Effect of Antithrombotic Therapy on Clinical Outcomes in Outpatients With Clinically Stable Symptomatic COVID-19: The ACTIV-4B Randomized Clinical Trial. JAMA. 2021 Nov 2;326(17):1703-1712.

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