



Hepatic Vein Thrombosis in a COVID-19 Patient with Hereditary Thrombophilia: A Case Report

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Abstract

Background: COVID-19 is an infection secondary to the novel SARS-COV-2 virus with a well-established increased risk for thrombotic events. However, the interaction between COVID-19 and other patient-specific hereditary or acquired thrombophilias remains a poorly explored area.

Case Report: We herein report a case of a 23-year-old Caucasian female with known risk factors for coagulopathy (smoking, oral contraceptives, anti-phospholipid (aPL) antibodies, heterozygous factor V Leiden mutation, and homozygous methylenetetrahydrofolate reductase (MTHFR) mutation) who developed a Budd-Chiari syndrome after testing positive for COVID-19. To our knowledge, this is the first report of a case of splanchnic vein thrombosis in a COVID-19 patient with the above risk factors.

Conclusion: Such a presentation underscores the additional increased thrombotic risk attributed to COVID-19 infections in the setting of underlying hereditary or acquired thrombophilias.

Keywords: Factor V Leiden, MTHFR mutation, Thrombophilia, COVID-19, Case Report

Introduction

COVID-19 is a respiratory tract infection that can involve multiple organ systems through a coagulopathy-related mode of injury [1,2]. Thrombosis in the setting of COVID-19 is a well-documented phenomenon; however, COVID-19-induced coagulopathy in patients with inherited thrombophilia remains a poorly explored topic in the English-speaking literature. Furthermore, thrombophilias can be autoimmune in nature, like the antiphospholipid syndrome (aPL) [3], or due to inherited conditions like Factor V Leiden mutation and hyperhomocysteinemia, which is caused by methylenetetrahydrofolate reductase (MTHFR) mutation [4].

Factor V Leiden mutation, the commonest inherited hypercoagulability disorder in Caucasians, is responsible for producing an aberrant copy of Factor V coagulation factor that is resistant to degradation; thus conveying a higher risk for thrombus formation. Factor V mutations are known to potentiate the effect of MTHFR on deep vein thrombosis [5]. COVID-19 related thrombosis, on the other hand, is related to viral-induced endothelial damage, leading to the activation of downstream coagulation mediators and ultimately thrombosis [6].

Case Presentation

We present the case of a 23-year-old Caucasian lady, smoker (daily water-pipe for three years), on hormonal contraception (norethindrone 5 mg for seven years, two tabs for five days every seven weeks), who presented initially to the emergency department for severe acute right upper quadrant pain. Initial blood workup (including complete blood count with differential, prothrombin time, and partial thromboplastin time) was not significant.

A Computed Tomography (CT) scan of the abdomen and pelvis at presentation illustrated the absence of contrast opacification of the right and middle hepatic veins with surrounding hepatic parenchyma edema, which is suggestive of Budd-Chiari Syndrome (Figure 1).



Figure 1 Axial contrast enhanced portal phase CT image showing thrombosis of the right (red arrow) and middle (black arrow) hepatic veins that appear dilated and non-opacified. Mild periportal edema is also noted.

In addition, findings on lung CT scan, such as the presence of interval appearance of bilateral peripheral rounded ground glass opacities in both lower lobes, were highly suggestive of COVID-19 infection (Figure 2). The diagnosis of COVID-19 infection was subsequently confirmed by a positive COVID-19 polymerase chain reaction (PCR) test.

She was discharged from the emergency department on a therapeutic subcutaneous enoxaparin dose (1 mg/kg twice daily) and referred to our service. Additional hereditary thrombophilia workup, ordered for the atypical presentation of COVID-19 related coagulopathy, revealed mutated genes for Factor V Leiden (heterozygous) and MTHFR (homozygous), and the presence of high titers of antiphospholipid antibodies (Table 1).

Workup revealed a homocysteine level of 35 $\mu\text{mol/L}$, cardiolipin antigen (Ag) immunoglobulin (Ig) M of 40 IgM Phospholipid Units (MPL), cardiolipin ag IgG <15 IgM Phospholipid Units (GPL), Beta-2 glycoprotein antibodies IgM, IgG, IgA of 47 U/mL, and a D-dimer level of 5.03 $\mu\text{g/mL}$. Her symptoms completely resolved within one week of starting anticoagulation. She will repeat CT scans of the abdomen in 6-9 months, and discussion regarding longer anticoagulation treatment will be discussed at that time based on the radiologic findings.

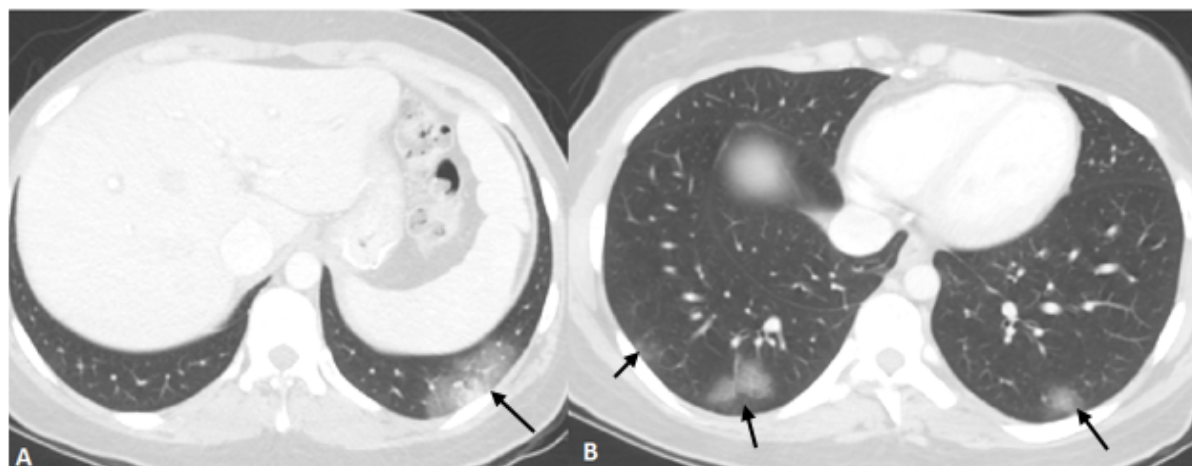


Figure 2: Axial CT scan images of the lower cuts of the chest (lung window) showing bilateral peripheral ground glass opacities associated with subtle interstitial intralobular septal thickening and lobular consolidation, typical for COVID-19 infection.

Table 1: Laboratory findings

Ab= antibody, IgM= immunoglobulin M, IgG= immunoglobulin G, IgA= immunoglobulin A, MPL= IgM phospholipid units, GPL= IgG phospholipid units.

Parameter	Value	Normal Values
Homocysteine level	35 µmol/L	5-15 µmol/L
Cardiolipin Ab IgM	40 MPL	<10 MPL
Cardiolipin Ab IgG	<15 GPL	<15m GPL
Beta-2 glycoprotein Abs IgM, IgG, IgA	47 U/mL	<20 U/mL
D-dimer	5.03 µg/mL	< 0.5 µg/mL

Discussion

COVID-19 has been reported as a risk factor for thrombosis, especially of the splanchnic vessels. Previously published cases have reported thrombosis of the portal vein [7,8], right hepatic vein and splenoportal axis [9], simultaneous thrombosis of the right portal vein, and of the proximal superior mesenteric artery and jejunal artery [10], as well as the

report of palmar digital vein thrombosis [11], and cerebral vein thrombosis [12].

COVID-19 can be the sole risk factor for splanchnic venous thrombosis, as illustrated in a case of portal vein thrombosis reported by Franco-Moreno et al, in which exhaustive workup for other risk factors was negative [13]. However, most cases of splanchnic vein thrombosis in COVID-19 were associated with at least one other risk factor, which includes factor V Leiden mutation [11], type 2 diabetes mellitus [9], essential thrombocythemia [7], and sepsis [8]. Other reported risk factors include aPL antibodies [12]. However, these antibodies can be seen in viral infections including cytomegalovirus, human immunodeficiency virus, varicella zoster virus [12], and other critical illness or vascular liver disease [9]. Moreover, the role of aPL antibodies in COVID-19 coagulopathy is unclear, and physicians should be cautious in the interpretation of aPL antibody titers in the setting of COVID-19 infection [13].

The case reported here presented is unique as the patient had multiple simultaneous and synergistic prothrombotic risk factors, both acquired and inherited. They included smoking, hormonal contraceptive use, anti-cardiolipin, anti-β2 glycoprotein antibodies, heterozygous factor V Leiden mutation, and homozygous MTHFR mutation. These

thrombus-predisposing conditions have distinct pathophysiology. Factor V Leiden is related to a mutant factor V that is less sensitive to the inhibitor effect, while MTHFR is related to a metabolic alteration leading to thrombosis [4,5]. Nevertheless, we hypothesize that the endothelial changes induced by the COVID-19 virus amplify the risk of patients with inherited and acquired blood clot-forming disorders for developing thrombotic events. To our knowledge, this is the first reported case of splanchnic vein thrombosis in a COVID-19 patient with an underlying MTHFR mutation. Also, no case reported to date has been associated with as many predisposing factors, which implies the possible need to administer anticoagulants for a prolonged period of time (perhaps indefinitely).

Clinicians must maintain a high index of suspicion for splanchnic vein thrombosis, which may be a late complication or even a presenting symptom in COVID-19 [14]. Some experts have even suggested doing whole-body CT scans in arterial and venous phases for any COVID-19 patient with abdominal pain or pulmonary embolism [10]. Up to 31% of ICU patients with COVID-19 develop thrombotic complications, even with prophylaxis; in many of these cases, predisposing factors are found eventually [9]. The most common thrombotic event in COVID-19 is believed to be venous thromboembolism [15]. Initial COVID-19 coagulopathy often presents with a prominent elevation of D-dimer (as was seen in our patient) and fibrin/fibrinogen degradation, and worse outcomes have been associated with higher D-dimer levels [16].

Conclusion

In conclusion, a 23-year-old lady presented for right upper quadrant pain, and was revealed to have a splanchnic vein thrombosis that could be secondary to either COVID-19 coagulopathy or to a positive status for antiphospholipid syndrome, and factor V Leiden and MTHFR mutations.

Cases like the one presented above raise the question of how much additional thrombosis

risk COVID-19 contributes to a patient with underlying hypercoagulability. Further research is required to assess the need to adjust anti-coagulation therapy for COVID-19 patients who happen to have genetic or other underlying inherited and/or acquired thrombophilia.

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