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.

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Case report

Cirrhosis and COVID-19: Diffuse venous thrombosis and its clinical implication

Mehtap Canastar[a], Kenji Okumura[b,*], Roxana Bodin[a,b], Anthony Gilet[c], Abhay Dhand[b,d]

[a] Gastroenterology and Hepatology, Westchester Medical Center / New York Medical College, Valhalla, United States
[b] Surgery, Westchester Medical Center / New York Medical College, Valhalla, United States
[c] Radiology, NY IMAGING Specialists, Port Jefferson Station, United States
[d] Medicine/Infectious Diseases, Westchester Medical Center / New York Medical College, Valhalla, United States

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ABSTRACT

A 60-year-old woman with Hepatitis C infection, cirrhosis, recurrent hepatic hydrothorax, and hepatocellular carcinoma was hospitalized with Coronavirus disease-2019 (COVID-19). After her initial discharge, she was re-admitted three weeks later with decompensated liver disease. Imaging revealed extensive thrombosis in the portal vein, superior mesenteric vein, splenic vein and bilateral brachial veins. Given the acute onset and extent of the thrombosis, the patient received therapeutic anticoagulation despite elevated prothrombin time/ international normalized ratio, thrombocytopenia and low fibrinogen.

Cirrhotic patients with COVID-19 maybe at high risk of thrombosis, which can present with significant hepatic decompensation.

Introduction

Critically ill patients who are hospitalized with COVID-19, are at increased risk of thrombosis despite administration of prophylactic anticoagulation [1,2]. Thromboembolism in COVID-19 is likely due to a combination of severe inflammatory response, critical illness, and hypoxemia [1,2]. Pulmonary embolus is the most common thrombotic complication, and others include deep vein thrombosis of the lower extremity, catheter related thrombosis of the upper extremity, ischemic stroke and arterial thrombosis [2]. Coagulation disorders in cirrhosis are associated with increased risk of both thrombosis and bleeding [3]. Deficiency of the coagulation factors that are produced in liver and changes in pro fibrinolytic factors leads to thrombosis at the same time thrombocytopenia, platelet dysfunction, deficiency of anti-fibrinolytic factors leads to bleeding in patients with liver disease [4]. We report our experience in management of a cirrhotic patient with COVID-19 who developed extensive venous thrombosis involving bilateral brachial veins, portal vein, superior mesenteric vein and splenic vein. While portal vein thrombosis (PVT) is a well-known complication in patients with advanced cirrhosis, there are no known reported cases of such extensive and diffuse venous thrombosis. We also discuss the clinical implications of new onset thrombosis in patients with cirrhosis as well as the diagnostic and therapeutic dilemmas while treating these events.

Case presentation

We report the hospital course in a 60-year-old woman with Hepatitis C virus (HCV) cirrhosis complicated by hepatic hydrothorax, hepatic encephalopathy, and hepatocellular carcinoma (HCC), and with recent diagnosis of COVID-19. During her initial hospitalization with shortness of breath, she received antibiotics, thoracentesis and chest tube placement for recurrent hepatic hydrothorax. In the setting of new fever, cough, persistent shortness of breath and hypoxemia she tested positive for COVID-19 based on a positive polymerase chain reaction test from the nasopharyngeal specimen. She received supportive care, COVID convalescent plasma and was discharged after improvement in clinical status after 10 days of hospitalization. At time of discharge her total bilirubin was 8 milligrams (mg) per deciliter (dL), platelet count was 33 thousand per cubic milliliter (k/mm3) and international normalized ratio (INR) was 1.49. Four weeks after the diagnosis of COVID-19, she was re-admitted with abdominal pain, acute kidney injury (AKI), severe hyponatremia, hyperkalemia, significantly elevated aspar-

Abbreviations: COVID-19, Coronavirus disease-2019; DIC, disseminated intravascular coagulation; HCC, hepatocellular carcinoma; HCV, Hepatitis C virus; MRI, magnetic resonance imaging; PVT, Portal vein thrombosis; SMV, superior mesenteric vein.

* Corresponding author.
E-mail address: kenji.okumura@wmchealth.org (K. Okumura).

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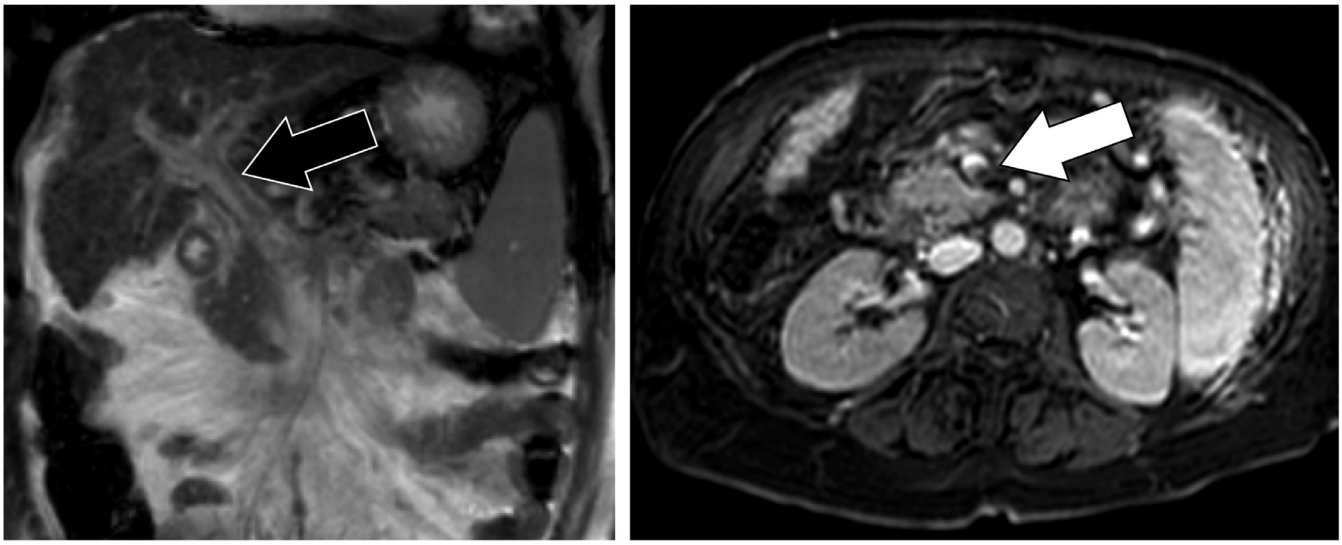

Fig. 1. Images showing portal vein thrombosis and superior mesenteric vein thrombosis. Fig. 1A–Black arrow showing portal vein thrombosis; Fig. 1B–White arrow showing superior mesenteric vein thrombosis.

tate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and total and direct bilirubin. Total bilirubin was 2 mg/dL prior to COVID-19 diagnosis, 6-8 mg/dL at the time of COVID-19 diagnosis and 28 mg/dL at time of re-admission. Given her history of HCC and worsening hyperbilirubinemia, an magnetic resonance imaging (MRI) of the abdomen done 37 days after diagnosis of COVID-19 revealed a liver with nodular contour and numerous regenerative nodules, prior ablation in segments 1, 5 and 8 without residual arterial enhancement, new extensive thrombosis of the portal vein (PV) with involvement of the superior mesenteric vein (SMV) and extension to the main, right, and left portal veins, and the splenic vein was also occluded (Figure 1).

Bilateral upper extremity duplex ultrasound showed bilateral brachial vein thrombosis. Patient was not on chemical thrombosis prophylaxis - due to platelet counts less than 50 k/mm^3 and fibrinogen less than 100 mg/dL. Subsequently the patient was started on therapeutic dose unfractionated heparin drip. During the six weeks of hospitalization, the patient remained hospitalized on treatment with low dose unfractionated heparin with some difficulty in heparin dosing due to frequent supra-therapeutic partial thromboplastin time (PTT), persistent low fibrinogen (<100 mg/dL) and low platelet count (<50 k/mm^3). Total and direct bilirubin remained elevated, 27 mg/dL and 17 mg/dL. She was subsequently discharged on low dose coumadin.

Discussion

Portal vein thrombosis (PVT) is common in patients with hepatobiliary malignancy and cirrhosis and is associated with the severity of the liver disease and presence of portal hypertension. In addition, underlying coagulation disorder such as Factor V Leiden, prothrombin gene mutations are more common in patients with cirrhosis and PVT [3]. The treatment of acute PVT aims to achieve recanalization in the case of complete obstruction, prevent progression of the thrombus, prevent intestinal ischemia and prevent onset/worsening of portal hypertension and variceal bleeding, role of treatment in chronic PVT is unclear. The most feared complication of anticoagulation for PVT is bleeding, especially variceal bleeding. Given bleeding risk and unclear benefit in with chronic PVT decision to treat depends on if PVT is acute vs chronic, presence of symptoms, SMV involvement and transplant listing status [4]. Similarly in patients with cirrhosis and COVID-19, the risk of portal venous thrombosis has been described in a small number of clinical studies [5,6]. In a meta-analysis of 5 studies which included 116 patients, biopsy and autopsy results estimated that vascular thrombosis was seen in 29.4% (95% Confidence Interval: 0.4-87.2) of the study patients [7]. COVID-19 has also been associated with development of PVT in non-cirrhotic patients. In a systematic analysis from 34 studies, 40 cases of portal venous thrombosis were described after COVID-19 or after COVID-19 vaccination [8]. In these cases, the most common clinical presentation was abdominal pain and most of the patients improved with therapeutic anticoagulation and were successfully discharged [8].

Our patient presented uniquely with acute extensive thrombosis not only in the portal vein but also in SMV, splenic vein, and bilateral upper extremity veins four weeks after the initial diagnosis of COVID-19. Our case highlights the risk of acute and extensive thrombosis in patients with cirrhosis and concurrent COVID-19, which can be associated with significant hepatic decompensation. Clinicians should have low threshold for investigating for thromboembolic events in patients with COVID-19 and cirrhosis in setting of unexplained clinical worsening. Blood D-dimers have been used during the current COVID pandemic to help with diagnosis of clinical and sub-clinical thrombotic events [9]. In patients with cirrhosis, the levels of blood D-dimer are significantly increased. These levels are further elevated in patients with severe liver dysfunction, the presence of ascites and the presence of portal vein thrombosis [10]. Therefore serial D-dimer values, along with an early clinical suspicion could help guide further diagnostic testing to evaluate for regional or systemic thrombosis in patients with cirrhosis along with additional risk factors like COVID-19 and/or HCC. Decision to treat with anticoagulation depends on previously described factors including location, extent and chronicity of the thrombus, symptoms, overall patient condition, transplant status and concern for active bleeding. If a decision is made to treat the patient with anticoagulation, then close monitoring for bleeding, thrombocytopenia, disseminated intravascular coagulation (DIC) is essential. Perhaps, such high-risk patients may benefit from prophylactic anticoagulation after carefully weighing against the risk of bleeding.

Conclusions

Patients with advanced liver disease who are hospitalized with COVID-19, are at risk of developing new onset thrombosis along with their pre-existing increased risk of bleeding. In our case report, we presented the findings associated with new onset of disseminated thrombotic events in a patient with advanced cirrhosis which was associated with significant hepatic decompensation. Similar to our patient, incidence of thrombosis in some cirrhotic patients who develop COVID-19 is likely higher, with the presence of additional risk factors like hepatocellular carcinoma, long standing indwelling central venous catheters, prolonged immobilization, and advanced liver disease with portal hypertension. A low threshold to perform a diagnostic test to investigate for thromboembolism can help prevent further hepatic decompensation in patients with chronic liver disease. Decision to treat a cirrhotic patient who is hospitalized with COVID-19 using prophylactic or full dose anticoagulation is very complex and has to be individualized to weigh against the increased risk of bleeding. Further studies are warranted to understand the role of cumulative risk factors for thrombosis in patients with cirrhosis and COVID-19.

Patient consent

Consent to publish the case report was not obtained. This report does not contain any personal information that could lead to the identification of the patient.

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Authorship

All authors attest that they meet the current ICMJE criteria for authorship. MC, RB and AD contributed to study initiation, study design, and writing of the manuscript. KO and AG contributed to critical revision of article and writing of the manuscript. All the authors approve the final manuscript.

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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.

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