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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Correspondence

Splanchnic vein thrombosis in COVID-19: A review of literature

Dear Editor,

Coronavirus disease-2019 (COVID-19) caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) can predispose to both venous and arterial thromboembolism [1–4]. Splanchnic vein thrombosis (SVT) including portal, mesenteric, splenic vein thrombosis and the Budd-Chiari syndrome, is a manifestation of unusual site venous thromboembolism. SVT usually occurs in association with cirrhosis, liver malignancy or in patients with inherited or acquired thrombophilia [5]. Limited literature is available regarding SVT in COVID-19. We did an extensive literature review on COVID-19 associated SVT. We searched PubMed for this literature review using search terms 'COVID-19 and splanchnic vein thrombosis, 'COVID-19 and portal vein thrombosis', 'COVID-19 and mesenteric vein thrombosis', COVID-19 and Budd-Chiari syndrome', COVID-19 and hepatic vein thrombosis' and 'COVID-19 and splenic vein thrombosis'. All the case reports with COVID-19 associated SVT so far were reviewed, and relevant data was abstracted from these studies. COVID-19 diagnosis was made by PCR assay except in one patient it was negative (suspected COVID-19).

The clinical features, laboratory values and outcome are summarized in Table 1 [6–11]. We found total of six patients. The median age of patients was 58 years (range 27–79 years) and 50% were male. Presenting symptoms were vomiting, abdominal pain, diarrhea, fever, shortness of breath, jaundice and altered mental status. None of the patients had cirrhosis or hepatocellular cancer. Work up done to rule out known associated inherited or acquired prothrombotic states in each case is outlined in Table 1. *One of the patients was diagnosed with essential thrombocytosis (myeloproliferative neoplasm), a known risk factor for SVT.* The diagnosis of SVT was made by computed tomography. SVT can occur as a presenting feature or a late complication of COVID-19. Five patients were diagnosed on day 1 of presentation and one patient was diagnosed on day 6. Portal vein was involved in all the patients, superior mesenteric in two while splenic vein and hepatic vein in one. One patient had concurrent superior mesenteric and jejunal artery thrombosis. All patients were started on anti-coagulation. Out of six, two patients died.

The exact pathological mechanism leading to the complication of SVT in COVID-19 is not well understood at present, possibilities include - viral infection of the endothelial cell leading to diffuse endothelial inflammation or increased procoagulant factors like factor VIII, von Willebrand factor, fibrinogen or virus induced cytokine storm leading to coagulation and fibrinolysis activation [12–14]. Additional explanations for the hypercoagulability may be the presence of high numbers of prothrombotic circulating microvesicles which are cytoplasmic microparticles stemming from platelets or monocytes and Neutrophil external traps (NETs) released from activated neutrophils, constitute a mixture of nucleic DNA, histones and nucleosomes [14]. The cause of SVT should be investigated systematically. The goal of treatment of acute SVT is to recanalize the obstructed veins, which will prevent complications-intestinal infarction, liver injury and portal hypertension. Clinicians should be aware of this unusual manifestation of COVID-19 so that prompt and appropriate interventions can be undertaken if it is suspected or confirmed.

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Table 1
Summary of clinical characteristics and outcomes of COVID-19 patients with splanchnic vein thrombosis.

Author	Franco-Moreno et al. [6]	Ofosu et al. [7]	La Mura et al. [8]	Del Hoyo et al. [9]	de Barry et al. [10]	Ignat et al. [11]
Country	Spain	U. S. A	Italy	Spain	France	France
Age/ex	27 M	55 M	72 M	61 F	79 F	28 F
Medical history	None	Hyperlipidemia	Parkinson disease, anxious-depressive syndrome, and mild vascular dementia	Type 2 diabetes mellitus	None	ET
Presenting sign and symptoms	Abdominal pain	Fever, shortness of breath, and altered mental status.	Fever, jaundice, and obnubilation.	Abdominal pain, vomiting	Fever, epigastric abdominal pain	Abdominal pain and vomiting
Wbc (10^9/L)/Hb (g/dL)/ Platelets (μL)	18/wnl/458	9.5/14/518	19.7/13.8/166	NR/NR/46	12.6/NR/NR	NR/NR/NR
ALP (U/L)/AST U/L)//ALT U/L)//Total. Bilirubin (mg/dL)	148/64/111/wnl	64/50/36/0.8	148/NR/257/7.79	NR/155/313/NR	NR/NR/NR/NR	NR/NR/NR/NR
D-dimer (μg/L)/CRP mg/dL	9.5/24.5	>44/3	101,087/17.2	4399.80/0.9	NR/12.5	NR/NR
PT/INR/PTT	wnl/wnl/wnl	NR/1.2/NR	1.27/NR/0.95	NR/NR/NR	NR/NR/NR/NR	
Site of thrombosis	Portal vein thrombosis	Portal vein thrombosis	Portal vein thrombosis	Thrombosis of the spleen- portal axis and hepatic vein	Portal vein and superior mesenteric vein thrombosis	Superior mesenteric and portal vein thrombosis
Imaging modality used for diagnosis	CT	CT	CT	CT	CT	CT
Day of diagnosis	Day 1	Day 1	Day 6	Day 1	Day 1	Day 1
Work up done for associated inherited or acquired prothrombotic states	Antiphospholipid antibody, Protein C and S, Antithrombin, factor VIII levels were normal, Flow cytometry for PNH was negative, BCR-ABL, JAK-2, Factor V Leiden and prothrombin G20210A mutations were not detected, Hepatitis A, B, C, HIV, CMV, EBV and HSV were negative, ANA, Anti-dsDNA, anti-double stranded DNA, anti-extractable nuclear antigen, ANCA, AMA, ASMA, anti-LKM-1were negative.	Antithrombin, lupus anticoagulant, protein C, and protein S were normal	Levels for protein C, Antithrombin, Factor 2 and Factor VIII were normal. Negative for hep B and C	Lupus anticoagulant antibodies were detectable at low titer, but V617F Jak-2, Factor V Leiden, prothrombin gene mutations anti-cardiolipin IgG and anti–β2-glycoprotein were negative.	NR	NR
Other sites of thrombosis	None	None	None	None	Superior mesenteric artery and jejunal artery	None
Treatment	Enoxaparin inpatient followed by acenocoumarol outpatient	Apixaban	Enoxaparin	Enoxaparin	AC	AC
Treatment of COVID-19	Hydroxychloroquine, azithromycin	Hydroxychloroquine, azithromycin	NR	NR	NR	NR
Outcome	Discharged	Discharged	NR	Died	Died	Discharged

Wbc white blood cells, Hb hemoglobin, ALP alkaline phosphatase, AST aspartate transaminase, ALT alanine transaminase, CRP c-reactive protein, PT prothrombin tine, INR international normalized ratio, PTT partial thromboplastin time, M male, F female, wnl within normal limits, CT computed tomography, PNH paroxysmal nocturnal hemoglobinuria, CMV cytomegalovirus, EBV Epstein-Barr virus, HSV herpes simplex virus, ANA anti-nuclear antibody, ANCA anti neutrophil cytoplasmic antibody, AMA anti mitochondrial antibody, ASMA anti smooth muscle antibody, anti-LKM-1 antiliver kidney microsomal antibody, NR not reported, SIH still in hospital at the writing of respective manuscript, AC anti-coagulation, Reference values- Wbc 4–10 10^9/L)/, Hb 12–15 g/dL, platelets 150–400 $\times$ 10^3μL, ALP 40–109 U/L, AST 5–40 U/L, ALT 9–59 U/L, Total. Bilirubin 0.1–1.1 mg/dL, D-dimer <500 μg/L, CRP <0.5 mg/dL.

Conflict of Interest

None of the authors have conflicts of interest.

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