Extrahepatic portal vein thrombosis in a pregnant patient with COVID-19: a rare thrombotic event survivor

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SUMMARY
A COVID-19 infection predisposes the infected person to thrombotic events. Myocardial infarction, acute limb ischaemia, mesenteric artery thrombosis and pulmonary embolism are all well-documented complications of this infection. Here we describe a pregnant patient who presented with obstructed labour with asymptomatic COVID-19 infection and developed ascites during the postoperative period. Further work-up of the patient revealed portal hypertension due to portal vein thrombosis (PVT). As the patient was healthy before this index pregnancy, a causative link between COVID-19 and PVT cannot be ruled out. Her COVID-19 infection progressed to a moderate disease. She was managed with steroids and appropriate antibiotics for secondary bacterial peritonitis. She was finally discharged after 2.5 months of multidisciplinary treatment. This is a case of a survivor of complications due to pregnancy, COVID-19 and extrahepatic portal vein obstruction.

BACKGROUND
Extrahepatic portal vein thrombosis (EHPVT) is an obstruction of the extrahepatic vein with or without involvement of the intrahepatic portal vein or the splenic or superior mesenteric veins.1 Globally, cirrhosis of the liver is the foremost cause of portal hypertension, followed by extrahepatic portal vein obstruction (EHPVO). In developing countries EHPVO accounts for 35%–40% of cases of portal hypertension. Most cases of non-cirrhotic portal vein thrombosis are caused by more than one factor, with thrombophilic conditions accounting for 60% of cases. Pathophysiological research revealed that a COVID-19 infection is a cause of thrombosis, and therefore if anyone develops COVID-19 during pregnancy the patient will have higher chances of thrombotic events.

CASE PRESENTATION
A 28-year-old primigravida was referred to a tertiary care dedicated COVID-19 hospital as a case of full-term pregnancy with asymptomatic COVID-19 infection. On examination, her vitals were stable with mild hypertension (150/90 mm Hg) and generalized body swelling. Obstetric examination revealed a single live fetus with features of obstructed labour. Hence, the patient was taken for emergency lower segment caesarean section. A healthy baby of birth weight 3.0 kg with Apgar score of 9/10 was delivered.

The immediate postoperative period was uneventful. Antibiotics (ceftriaxone and metronidazole), low molecular weight heparin (LMWH) and supportive treatment as per the COVID-19 treatment protocol were prescribed to the patient. On postoperative day (POD) 5, the patient complained of acute abdominal pain. Her abdomen was distended and tender and abdominal girth showed an increasing trend. The surgical site was also found to be indurated. She later developed high-grade fever. Antibiotics were upgraded to piperacillin-tazobactam. The patient was subjected to ultrasonography (USG) of the abdomen and further to contrast-enhanced CT (CECT) of the abdomen.

The USG showed a liver span of 12.8 cm. The main portal vein was not visualised, no flow on colour Doppler could be appreciated, periportal cuffing was present, and the portal vein at the hilum was replaced by multiple tortuous collaterals. Neither the intrahepatic biliary radical dilatation nor surface irregularity of the liver was evident. The spleen was enlarged (14.7 cm), with multiple dilated collaterals at the splenic hilum, suggestive of EHPVO. Gross ascites and bilateral minimal pleural effusion were also seen (figure 1).

CECT further confirmed these findings, along with an incision site haematoma which was planned to be managed conservatively (figure 2).

Various laboratory reports are elaborated sequentially in table 1.

On POD 7, the patient was transferred to the intensive care unit in view of tachypnoea, fever and ascites. Ascsitic fluid examination showed a higher Total Leucocyte Count (TLC) count of 4000 cells/mm³ with 60% neutrophils and low Adenosine deaminase (ADA). Serum ascitic albumin gradient was >1.1 and Gram staining and Ziehl-Neelsen (ZN) staining showed no micro-organism except for a few pus cells. Blood culture and ascitic fluid culture were sterile, so a diagnosis of secondary bacterial peritonitis (postcaesarean section) with severe anaemia and thrombocytopaenia secondary to non-cirrhotic portal vein thrombosis was made. Wound dehiscence was present with wound site haematoma, which was managed by daily sterile surgical dressing. To relieve abdominal discomfort and breathlessness, she required intermittent therapeutic paracentesis. LMWH was stopped in view of the thrombocytopaenia. Carvedilol 3.125 mg, spironolactone 200 mg and ramipril 2.5 mg were started.
On POD 10, she developed hypoxia and required 2 L/min oxygen to maintain an oxygen saturation of >94%. She developed crepitations, mostly in the bilateral infrascapular region. She was started on 6 mg dexamethasone according to our institutional guidelines for moderate COVID-19. According to Institutional guidelines, she was started on 6 mg oral dexamethasone, injection meropenem and injection cindamycin. On POD 15, she had one episode of haematemesis, which was managed with pantoprazole infusion and terlipressin. Upper gastrointestinal endoscopy could not be done due to technical reasons during the COVID-19 period. Her oxygen requirement continued to increase further up to 6 L/min by face mask. Her condition improved gradually with the treatment. On POD 21, repeat ascitic fluid analysis showed total cell count of 100/cu mm with 80% mononuclear cells. On POD 30, her ascites began to subside and the wound haematoma resolved. The patient was maintaining oxygen saturation of >95% in room air. She received a total of 8 units of packed red blood cells (PRBC), 4 units of platelet concentrates and 12 doses (100 mL) of 20% albumin during her hospital stay.

On POD 56, the patient again developed high-grade fever and her USG revealed 500–600 cc of thick intraperitoneal collection. Doppler showed persistence of thrombus in the portal vein. USG-guided pigtail catheter was inserted to drain the collection and antibiotics (meropenem and levofloxacin) were given. After 64 days of hospitalisation, the patient was discharged in stable condition. The patient is still under follow-up and is in stable condition.

DIFFERENTIAL DIAGNOSIS
Undiagnosed chronic liver disease, tuberculous ascites and Budd-Chiari syndrome are the main differentials. USG of the abdomen and ascitic fluid evaluation narrowed down the diagnosis.

TREATMENT
The patient was managed with LMWH, diuretics, beta blockers, terlipressin and antibiotics for secondary bacterial peritonitis.

OUTCOME AND FOLLOW-UP
The patient was discharged and followed up monthly through telemedicine services.

DISCUSSION
COVID-19 infection is associated with raised interleukin (IL)-2, IL-7, IL-10, granulocyte-colony stimulating factor, IgG-induced protein 10, macrophage chemoattractant protein-1, macrophage inflammatory protein-1 alpha and tumour necrosis factor-α. These cause a hypercoagulable state, possibly via activation of endothelial cells, platelets and leucocytes, inducing tissue factors and subsequently triggering clotting cascade by activation of factor VIIa. This will lead to various thrombotic events such as pulmonary venous thromboembolism, arterial thrombosis causing acute limb ischaemia, acute coronary syndromes and mesenteric ischaemia. When combined with pregnancy the chances of thrombotic events increase. While searching the literature, we did not come across any case report of EHPVT in COVID-19. This is probably the first case report of chronic EHPVT described in COVID-19 during pregnancy.

In 2011, Aggarwal et al reported their observations of pregnancy in patients with EHPVO. They observed 26 such pregnancies in 14 women and found that pregnancy outcome was successful if the disease is adequately controlled. In another retrospective study, a total of 50 pregnancies with non-cirrhotic portal hypertension were reported, in which 12 were due to EHPVO.

In a 9-year study from South India, an incidence of portal hypertension in pregnancy of 0.07% was observed, and in such patients non-cirrhotic portal hypertension accounts for 74.1% of cases. Of the patients, 54.7% were diagnosed with it along with an index pregnancy. Most of them presented with pancytopenia and splenomegaly. Variceal bleeding occurs in 25% of cases. Aetiological, adult-onset EHPVO is heterogeneous but may be associated with one or more risk factors for thrombosis, such as myeloproliferative disorders or deficiency of protein C and protein S. Aggarwal et al found underlying hypercoagulable states in 21% of patients, whereas Mandal et al and Subbailah et al did not find any such cause in any of their patients.

Patients with portal vein obstruction need detailed preconception counselling and evaluation. Liver functions usually remain well preserved in these patients but tend to decompensate in a few patients in the event of an increased portal blood flow and thrombogenic tendency during pregnancy. There are no definite guidelines for the management of such patients to date due to the paucity of evidence. Any history of variceal bleeding, jaundice, thrombocytopenia, ascites or hypersplenism indicates poor prognosis. Pregnancy should be planned in stable liver conditions and medical termination of pregnancy (MTP).
Extrahepatic portal vein obstruction is the most common cause of portal hypertension after chronic liver disease. Anticoagulation is the preferred treatment for these cases.

**Learning points**

- COVID-19 infection is a prothrombotic condition and pregnancy, being a hypercoagulable state, may act synergistically.
- Extrahepatic portal vein obstruction is the most common cause of portal hypertension after chronic liver disease.

**Contributors**

MA: patient care, manuscript writing. SS: patient care, collection of data. US: radiological assistance. DB: patient care, manuscript editing.

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**Table 1** Serial investigations of the patient

| Test                        | POD 0  | POD 5  | POD 15 | POD 30 | POD 50 | At discharge |
|-----------------------------|--------|--------|--------|--------|--------|--------------|
| Haemoglobin (g/L)           | 13.3   | 4.9    | 8.5    | 9.2    | 9.8    | 10           |
| White Blood Cell Count (cu mm) | 17000  | 20000  | 12000  | 8000   | 7640   | 6400         |
| Platelets (thousand/microliter) | 93     | 40     | 109    | 98     | 110    | 132          |
| PT (s)                      | 11.1   | 14.7   | 15.2   | 16.4   | 12.6   | 13           |
| INR (s)                     | 0.95   | 1.29   | 1.33   | 1.35   | 1.08   | 1.1          |
| APTT (s)                    | 35.5   | 41.4   | 29.3   | 30.4   | 28     | 29           |
| D-dimer (μg/mL)             | 3.60   | 4.41   | –      | 2.6    | 1.8    | 0.6          |
| Serum bilirubin (mg/dl)     | 1.89   | 3.20   | 2.7    | 1.3    | 1.4    | 0.8          |
| Serum albumin (mg/dl)       | 2.43   | 1.68   | 2.63   | 2.4    | 1.9    | 3.0          |

Viral markers (HBsAg, HCV and HIV), ANA, liver profile and thrombophilia profile were negative.

ANA, Anti nuclear antibody; APTT, activated partial thromboplastin time; HBsAg, Hepatitis B surface antigen; HCV, Hepatitis C virus; INR, International Normalized Ratio; POD, Post operative day; POD, postoperative day; PT, Prothrombin time.
