Spontaneous large liver haematoma with extensive intraperitoneal bleeding in a patient with COVID-19 infection

Busara Songtanin, Abbie Evans, Kenneth Nugent

BACKGROUND
Haemorrhagic complications during COVID-19 infections have been reported and are associated with an increased risk of overall and major bleeding. Hepatocyte infection by COVID-19 has also been reported, and pathologic studies indicate that SARS-CoV-2 causes cytopathy. In many critically ill patients, the history can be limited due to intubation and sedation, and patients cannot alert clinicians to new events. The physical examination provides important information, but laboratory tests and radiographic imaging studies are essential when a life-threatening complication, such as acute blood loss, occurs. Management decisions will depend on haemodynamic stability and extent of blood loss, and these patients may require surgery to control bleeding. The management of critically ill patients with COVID-19 on ventilators presents additional problems related to patient isolation and the frequent use of narcotics and sedatives. The patient in this case report developed an acute hepatic haemorrhage during a prolonged hospital course for respiratory failure management.

CASE PRESENTATION
A woman (G9P6026) in her early 40s with no previous medical history presented to the emergency department for induction of labour at 38 weeks for arrest of descent and non-reassuring fetal heart rate tracings. The patient had an uncomplicated lower transverse caesarean section; the newborn infant was vigorous, weighed 3410 g and had appearance, pulse, grimace, activity, and respiration (Apgar) scores of 9 at 1 min and 9 at 5 min. However, the patient reported fever and shortness of breath for 1 day when admitted and was positive for COVID-19 infection by PCR. At this time, she denied chest pain, abdominal pain or changes in bowel movements. Initial vital signs showed an O₂ saturation of 98%, and her O₂ saturations were normal during labour. Three days after she was diagnosed with COVID-19, her saturations dropped to 88% on room air, and she required 3 L of oxygen per minute by nasal cannula. She was subsequently diagnosed with COVID-19 pneumonia and later required intubation on hospital day 12. The patient was started on heparin at 5000 units every 12 hours for deep vein thrombosis prophylaxis. Her hospital course was complicated by acute respiratory distress syndrome, prolonged intubation and eventual tracheostomy on day 32.

On day 49 of hospitalisation, the patient had melena with no haematochezia and no haematemesis. Her haemoglobin dropped from 9.7 g/dL to 5.6 g/dL (figure 1). She had a blood pressure of 122/63 mm Hg and a heart rate of 110 bpm. She grimaced on abdominal palpation and had rebound tenderness. Melena was present on rectal examination, and her faecal occult blood test was positive. The nasogastric tube did not recover blood or a coffee ground material. Heparin was discontinued. The patient was sent for CT scans of abdomen and pelvis to rule out possible intraperitoneal bleeding. Additional laboratory tests showed platelets of 122 k/µL, sedimentation rate of 55 mm/hour and a C reactive protein (CRP) of 6.5 mg/dL.

A CT scan of the abdomen and pelvis showed a very large subcapsular hepatic haemorrhage with retroperitoneal extension. The surgery service was immediately consulted for possible laparotomy. A repeat CT scan of abdomen and pelvis with angiography 2 hours later showed no progressive bleeding, and the haematoma size remained stable. She received 4 units of packed red blood cells. Her lowest blood pressure that day was 96/45 mm Hg. The patient was managed non-operatively due to the stable haemoglobin after transfusion and imaging studies showing no increase in size of the haematoma.

SUMMARY
Thrombotic complications during COVID-19 infections occur frequently, and anticoagulants to prevent and treat deep vein thrombosis appear to have a good safety profile in these patients. In addition, haemorrhagic complications during COVID-19 infections have also been reported. Hepatic inflammation can occur in COVID-19 infections as a direct consequence of cellular infection and cytopathy. Spontaneous subcapsular hepatic haemorrhage is extremely rare and can be life-threatening.

A woman in her 40s presented to the hospital with fever and shortness of breath and was diagnosed with COVID-19 infection with respiratory failure requiring intubation. On day 49 of hospitalisation, she developed melena and acute anaemia; her haemoglobin dropped from 97 g/L (9.7 g/dL) to 56 g/L (5.6 g/dL). Abdominal and pelvic CT scans showed a large subcapsular liver haematoma with retroperitoneal extension. The patient received blood transfusions and remained haemodynamically stable. She was eventually extubated and discharged home.
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INVESTIGATIONS
Previous esophagogastroduodenoscopy on hospital day 40 for percutaneous endoscopic gastrostomy tube placement showed no gastric bleeding or ulcer. However, later in the hospital course, she had melena, and laboratory tests showed acute anaemia with haemoglobin decrease from 9.7 g/dL to 5.6 g/dL (see haemoglobin trend in figure 1) and a mean corpuscular volume 93 fL (reference value 79.4–94.8). Additional laboratory tests included platelet count of 345 k/µL, blood urea nitrogen 53 mg/dL, creatinine 0.3 mg/dL, alkaline phosphatase 173 U/L, alanine aminotransferase 125 U/L and aspartate aminotransferase 48 U/L (see aspartate aminotransferase (ALT) and aspartate aminotransferase trend in figure 2, see table 1 for lab summary 5 days before the bleeding event and 5 days after). The coagulation profile was normal with prothrombin time (PT) 12.5 s (reference 9.4–12.5), partial thromboplastin time (PTT) 27.5 s (reference 25.1–36.5) and international normalised ratio 1.10. Inflammatory markers included lactate dehydrogenase level 4 days before the bleeding event 176 ng/mL. A faecal occult blood test was positive. A single transfusion, the patient was managed non-operatively. The interventional radiology service did not identify any active bleeding sites, which might provide a non-surgical approach to treatment. The GI consultant did not think endoscopy and colonoscopy were warranted since patient appeared to be stable and had a normal esophagogastroduodenoscopy for percutaneous endoscopic gastrostomy tube placement 2 weeks before this event. In addition, she had no complications related to her pregnancy and her C-section. The most likely possibility was a direct effect of COVID-19 infection on the liver. The ALT levels increased prior to her bleeding event, and this could represent microvascular ischaemic injury in the liver related to COVID-19.

DIFFERENTIAL DIAGNOSIS
The most likely cause of acute anaemia in a patient requiring prolonged hospitalisation for acute respiratory failure without trauma is upper gastrointestinal bleed secondary to stress gastritis or ulceration. Other less frequent causes include renal haemorrhage, retroperitoneal bleeding and bleeding from hepatic rupture, splenic rupture or a rupture of a vascular aneurysm. An additional consideration in a patient who was postpartum is hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome. However, this patient did not have preeclampsia or eclampsia, did not have thrombocytopenia and developed acute hepatic haemorrhage over 40 days post C-section. The risk of bleeding from the anticoagulants is also a possible consideration but less likely due to low risk of bleeding from pharmacologic deep vein thrombosis prophylaxis with heparin 5000 units subcutaneous every 12 hours. The patient was not on any medication, which might have platelet effects and did not have oral mucosal bleeding, petechiae, ecchymoses or bleeding from intravenous catheter sites. The patient had a normal PT and PTT, normal platelet counts and normal renal function. These tests exclude other common causes of bleeding in critically ill patients. In addition, she had no complications related to her pregnancy and her C-section. The most likely possibility was a direct effect of COVID-19 infection on the liver. The ALT levels increased prior to her bleeding event, and this could represent microvascular ischaemic injury in the liver related to COVID-19.

TREATMENT
The patient was treated conservatively, and heparin was discontinued. She received 4 units of packed red blood cells; vital signs and serial haematocrits were monitored closely. Due to the stable size of the haemorrhage and the stable haemoglobin level after transfusion, the patient was managed non-operatively. The interventional radiology service did not identify any active bleeding sites, which might provide a non-surgical approach to treatment. The GI consultant did not think endoscopy and colonoscopy were warranted since patient appeared to be stable and had a normal esophagogastroduodenoscopy for percutaneous endoscopic gastrostomy tube placement 2 weeks before this event. In addition, the surgical consultant did not recommend endoscopy or a surgical procedure.

OUTCOME AND FOLLOW-UP
After the patient was transfused with four units of packed red blood cells; her haemoglobin increased to 9.7 g/dL 2 days after the bleeding. She was haemodynamically stable. The patient eventually had her tracheostomy removed, was discharged home on hospital day 60 and scheduled for an outpatient visit for PEG tube removal.

DISCUSSION
COVID-19 has been associated with haematological complications, including both thromboembolic events and bleeding diathesis. Al-Samkari et al analysed the frequency and severity of thrombotic and haemorrhagic complications in 400 hospitalised patients with COVID-19 who were receiving standard-dose prophylactic anticoagulation. The overall bleeding rate was 4.8% (21 episodes and 19 patients); the frequency was higher in critically ill patients. A reduced platelet count (<150 k/µL) and increased D-dimer levels (>2500 ng/mL) at presentation
predicted a bleeding complication during hospitalisation. The most frequent sites of bleeding were the GI tract and the lung. A literature review at the time of this case report was drafted identified only two documented cases of a spontaneous hepatic hematoma as a sequela to COVID-19.²³ Both cases were middle-aged women with no history of liver disease who presented with fever and were ultimately diagnosed with COVID-19. In both cases, right upper quadrant pain was present, and a spontaneous hepatic hematoma was found during evaluation. One patient was treated with percutaneous drainage of an hepatic hematoma. The second patient had very elevated liver enzymes and was treated with N-acetylcysteine.

The incidence of spontaneous hepatic hematoma is low, accounting for only 1% of admissions to specialist liver units.⁴ Various clinical disorders can cause these hematomas, and these...

| Table 1 | Lab summary 5 days before the bleeding event (hospital day 49) and 5 days after |
|---------|--------------------------------------------------------------------------------|
| Hospital day | 44 | 45 | 46 | 47 | 48 | 49 | 50 | 51 | 52 | 53 | 54 |
| ALT (IU/L) | 252 | 242 | 173 | 123 | 96 | 125 | 96 | NA | 57 | 55 | 47 |
| AST (IU/L) | 155 | 90 | 42 | 31 | 28 | 48 | 33 | NA | 21 | 26 | 29 |
| Hb (g/dL) | 9.2 | 9.5 | 9.2 | 8.7 | 9.7 | 5.5 | 9.5 | 9.2 | 9 | 9.2 | 8.8 |
| WBC (×10³/L) | 5.33 | 6.01 | 6.71 | 5.9 | 8.77 | 10.71 | 9.61 | NA | 10.96 | 10.86 | 10.12 |
| Pt (K/uL) | 301 | 256 | 268 | 241 | 311 | 341 | 281 | NA | 283 | 306 | 326 |
| BUN (mg/dL) | 24 | 32 | 41 | 36 | 22 | 53 | 36 | 36 | 36 | 31 | 33 |
| Cr (mg/dL) | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.3 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| PT (sec) | Ref 5–12.5 | 12.5 |
| Ref 9.4–12.5 | |
| PTT (sec) | Ref 25.1–36.5 | 27.5 |
| INR | Ref<1.1 | 1.1 |
| TB (mg/dL) | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.3 | 0.4 | 0.5 |
| LDH (IU/L) | Ref 135–225 | 292 |

ALT, alanine transaminase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; Hb, haemoglobin; INR, international normalised ratio; LDH, lactate dehydrogenase; Plt, platelet count; PT, prothrombin time; PTT, partial thromboplastin time; TB, total bilirubin; WBC, white cell count.

**Figure 3** CT scan of the abdomen without angiography shows large subcapsular haematoma.

**Figure 4** CT scan of the abdomen and pelvis with angiography shows hepatomegaly and subcapsular haematoma measuring 16.8 cm in craniocaudal dimension with extensive intraperitoneal bleeding into pelvis. The hepatic dimension was 26.64 cm in a craniocaudal axis.
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include hepatic adenomas, hepatocellular tumours, amyloidosis, systemic lupus erythematosus and warfarin therapy. The pathogenesis involves compromised integrity of the hepatic parenchyma and vasculature. This case study suggests that COVID-19 infection can cause hepatic injury. The pathogenesis is likely multifactorial and includes virus-induced hepatic cytotoxicity and apoptosis, elevated inflammatory cytokines leading to vascular damage and microthrombosis and possibly alterations in hepatic blood flow resulting in ischaemia and/or vascular congestion. Although anticoagulation could cause spontaneous hepatic hematoma, this seems unlikely in this patient. She had been on heparin for a month for venous thrombosis prophylaxis, and daily labs with a complete blood count had been routinely checked. In addition, low-dose prophylactic heparin is not associated with a statistically significant increase in major bleeding or fatal bleeding. Finally, the HELLP syndrome is a possibility in a postpartum woman but seems unlikely given the timeline for this acute hepatic haemorrhage and the persistently normal platelet counts.

While the exact aetiology and mechanism remain unknown, an association between COVID-19 and spontaneous hepatic hematoma is the best explanation for this complication in this patient. This complication adds to the clinical complexity in patients with severe COVID-19 infection and should be considered in these patients when they have a sudden change in clinical status and develop acute anaemia.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

ORCID iD
Busara Songtanin http://orcid.org/0000-0002-4117-4272

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