Acute oesophageal necrosis in a patient with recent SARS-CoV-2

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SUMMARY

A 57-year-old Hispanic man with diabetes presented with dyspnoea. He had a positive SARS-CoV-2 PCR. He was intubated for severe hypoxia and treated with intermittent pressors, methylprednisolone and supportive care. He was extubated on hospital day (HD) 9 and discharged to a skilled nursing facility (SNF) on HD 18. Approximately 1 month later, he presented with melena. Endoscopy revealed two large 1.5–2 cm wide-based distal oesophageal ulcers without active bleeding. Histology showed ulcerated squamous mucosa with extensive necrosis extending to the muscularis propria and coccoid bacterial colonies with rare fungal forms suggestive of *Candida*. He was treated with fluconazole and pantoprazole and was discharged to a SNF. Approximately 3 weeks later, he was readmitted for complications. Repeat endoscopy demonstrated improvement and histology revealed chronic inflammation with reactive epithelial changes. Incidentally, SARS-CoV-2 PCR was positive during this visit without any respiratory symptoms.

BACKGROUND

Acute oesophageal necrosis (AON) is a rare condition that classically appears as a circumferential black area in the oesophagus with the underlying aetiology being tissue hypoxia. SARS-CoV-2 disease (COVID-19) through dysregulation of inflammatory and coagulation mechanisms also causes tissue hypoxia. We report a case of AON presenting with gastrointestinal bleeding following a prolonged hospital stay for COVID-19. Many patients with COVID-19 receive anticoagulation due to their prothrombotic state, placing them at higher risk for gastrointestinal bleeding. AON should be considered as a potential cause of gastrointestinal bleeding in these patients.

CASE PRESENTATION

A 57-year-old Hispanic man presented to the emergency room with dyspnoea for 1 week. He had no relevant medical history, although later during the course of his hospitalisation was found to have diabetes (Hemoglobin A1c 7.5%). He had no surgical or family history and denied medication use. He did not have any alcohol, tobacco or recreational drug use. He was intubated secondary to severe hypoxia. Initial laboratory data revealed positive SARS-CoV-2 PCR, hyponatraemia, anion gap respiratory acidosis, elevated creatinine indicating acute kidney injury, mildly elevated transaminases, elevated inflammatory markers and neutrophil predominant leucocytosis. Chest radiograph demonstrated bilateral patchy airspace opacities. The D-dimer was elevated but secondary to reduced glomerular filtration rate (GFR), CT of the chest with intravenous contrast could not be done to rule out pulmonary embolism. Bilateral lower extremity ultrasound studies were negative for deep vein thrombosis (Investigations table 1). The patient received fluid resuscitation, pressor support with norepinephrine, intravenous cefepime and vancomycin (dosed as per GFR), intravenous methylprednisolone (40 mg every 8 hours), prophylactic dose of subcutaneous enoxaparin (dosed per GFR) and famotidine for gastrointestinal prophylaxis. Initially, he required high FiO_2 to maintain oxygen saturations but gradually showed improvement. Pressors were weaned off on hospital day (HD) 4. His electrolyte abnormalities and creatinine gradually improved. He had adequate urine output. On HD 7, he received convalescent plasma therapy. His chest radiograph continued to show moderate diffuse ground-glass opacities and diffuse peribronchial thickening bilaterally. Respiratory and blood cultures remained negative. He completed a 10-day course of broad-spectrum antibiotics and was gradually weaned off of methylprednisolone (3 weeks taper) after being successfully extubated on HD 9. His COVID-19 PCR test was still positive on HD 14. He was requiring supplemental oxygen via nasal cannula, which was weaned down to 4 L by the day of discharge on HD 18. Due to significant deconditioning from his prolonged hospitalisation, he was discharged to a skilled nursing facility (SNF). All of his inflammatory markers were decreasing at the time of discharge. Creatinine, though improved, was still elevated at discharge, suggesting development of or underlying chronic kidney disease.

Approximately 1 month after discharge, the patient developed melena, for which he was readmitted to the hospital. He had normal vital signs and oxygen saturation was 100% on room air. Physical examination exhibited generalised deconditioning but was otherwise unremarkable. The differential diagnosis included peptic ulcer disease given the preceding critical illness. Gastritis and oesophagitis from prolonged steroid use were considered to represent other possible aetiologies. The probability of Mallory-Weiss syndrome was low as there was no reported history of persistent vomiting. Angiodysplasia and mass lesions were also considered.

INVESTIGATIONS

The patient's haemoglobin on admission was 78 g/L and SARS-CoV-2 PCR was negative. Oesophagogastroduodenoscopy was performed, revealing

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Table 1 Investigations

Significant labs on admission of index hospitalisation	Significant labs on discharge of index hospitalisation	Significant labs on admission of 2nd hospitalisation
Sodium 116 mEq/L, potassium 4.9 mEq/L, chloride 82 mEq/L, bicarbonate 11 mEq/L, creatinine 3.70 mg/dL, bloodurea nitrogen 44 mg/dL, glucose 209 mg/dL and calcium 7.5 mg/dL.	Creatinine 2.43 mg/dL, blood urea nitrogen 95 mg/dL, hemoglobin 114 g/L, mean corpuscular volume 90.6 FL, mean corpuscular hemoglobin concentration 33.8 g/dL, white blood cells 3.9 L/CMM, platelets 80 × 10^9/L	Hemoglobin 73 g/L, mean corpuscular hemoglobin concentration 33.7 g/dL, platelets 314 x10^9/L, international normalized ratio 1.10, pro time 14.2 s.
Alanine transaminase 76 units/L, aspartate transaminase 61 units/L, alkaline phosphatase 115 units/L, total bilirubin 0.8 mg/dL, albumin 1.9 g/dL and globulin 5 g/dL.	Ferritin 1517 ng/mL, D-dimer 1.18 mcg/mL, <2.9 mg/L	Stool occult blood positive.
Lactate dehydrogenase 667 units/L, D-dimer 8.09 mcg/mL, international normalized ratio 1.17, pro time 15 s, lactic acid 10.5 mmol/L, procalcitonin 1.44 ng/mL, CRP 153 mg/L and ferritin 2431 ng/mL.	COVID-19 PCR positive.	COVID-19 PCR negative.
White blood cell count 20.7 K/CMM, 89.7% neutrophils, 7.6% lymphocytes and 1.7% monocytes. Hemoglobin 140 g/L and platelets 322 x10^9/L.		CT scan of abdomen/pelvis without contrast: colonic diverticulosis without diverticulitis.
Arterial blood gas pH 7.25, PCO_2 42 mm Hg, PO_2 73 mm Hg, HCO_3 12 mEq/L, SaO_2 85.4 on FiO_2 100%.		
Hemoglobin A1c 7.5%, brain naturetic peptide 412 pg/mL.		
COVID-19 PCR positive. Blood and respiratory cultures negative.		
Chest X-ray: bilateral patchy airspace opacities and a small right pleural effusion. Head CT: unremarkable. Bilateral lower extremity venous ultrasound studies: negative for deep vein thrombosis.		

two large 1.5–2 cm wide-based ulcers in the distal oesophagus without active bleeding (figure 1A). His haemoglobin remained stable after endoscopy. Histology of the oesophageal ulcer (figure 1B) revealed ulcerated squamous mucosa with extensive necrosis extending to the muscularis propria. Coccoid bacterial colonies and rare fungal forms suggestive of *Candida* species were seen in the necrotic areas. Cytomegalovirus and herpes simplex virus immunoperoxidase stains were negative.

TREATMENT

The patient was initially started on a pantoprazole intravenous drip and received 1 unit of packed red cells with an appropriate response in haemoglobin. After endoscopy, the pantoprazole intravenous drip was converted to pantoprazole 40 mg oral two times per day and fluconazole 200 mg oral daily for 14 days was added. He was tolerating a diet without any nausea, vomiting or abdominal pain. He developed urinary retention that was managed by Foley catheterisation and he was eventually discharged back to the SNF on HD 9.

OUTCOME AND FOLLOW-UP

Approximately 3 weeks later, the patient was readmitted to the hospital due to a urinary tract infection, *Clostridium difficile* diarrhoea and bilateral lower extremity deep vein thrombosis.

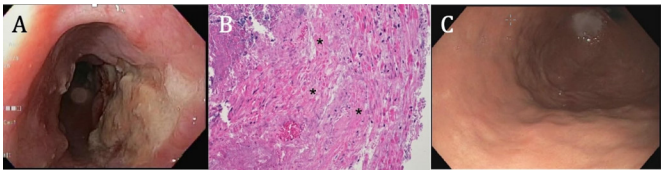

Figure 1 (A) Initial endoscopy demonstrated two wide-based 1.5–2 cm distal oesophageal ulcers. (B) Necrotic muscularis propria of the oesophagus (asterisk) with partially viable smooth muscle cells on the left side of the image (H&E stain, original magnification ×200). (C) Follow-up endoscopy (at 2 months) demonstrated healing ulcers.

He was significantly deconditioned and weak with severe protein-calorie malnutrition as demonstrated by a drop in his body mass index from 32 kg/m^2 at the index hospitalisation to 20 kg/m^2 on this admission. His oral intake and nutritional status remained poor during his treatment in the hospital. His albumin was 1.2 g/dL. A decision was made to proceed with placement of a percutaneous endoscopic gastrostomy tube for enteral nutrition. He tolerated this well. Repeat endoscopy at this time showed improvement in the oesophageal ulceration (figure 1C). Histology demonstrated squamous mucosa with chronic inflammation and reactive epithelial changes. Incidentally, SARS-CoV-2 PCR was positive during this visit without any respiratory symptoms. After clinical improvement, the patient was discharged home.

DISCUSSION

The WHO declared SARS-CoV-2 disease (COVID-19) a pandemic on 11 March 2020. The majority of cases are reported to be mild but 19% of patients present with severe symptoms. The overall estimated mortality is 2.3%. Similar to SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 is a beta-coronavirus. Bats are thought to be the most likely natural hosts. The virus, which then undergoes mutation or recombination in animal hosts, can infect humans. Pangolins have been implicated as the intermediate animal hosts of SARS-CoV-2.[1]

Although the most common presentation of COVID-19 is respiratory, gastrointestinal problems including diarrhoea and elevated transaminases have been frequently noted.[2] This can be easily explained by the wide distribution of the ACE2 receptor through which SARS-CoV-2 gains entry into target cells. ACE2 receptors are present in the oral mucosa, oesophagus, small intestine, colon, liver and spleen in addition to the respiratory system. Common gastrointestinal symptoms include diarrhoea, nausea, vomiting and lack of appetite.[3] Cases of ischaemic colitis,[4] bowel perforation,[5 6] paralytic ileus,[7] gastrointestinal bleeding[8 9] and

pneumatosis intestinalis[10] in patients with SARS-CoV-2 have been reported. Dysregulation of the renin angiotensin system, cytokine storm, oxidative stress and coagulation abnormalities with resulting tissue hypoxia seem to be the underlying mechanisms of the disease.[11] Additionally in the intestine, SARS-CoV-2 has been postulated to decrease tryptophan absorption via ACE2, causing alteration of the intestinal flora, a decrease in antimicrobial peptides and resultant mucosal inflammation.[12] Whether intestinal disease in SARS-CoV-2 is due to the primary infection or a secondary response from systemic inflammation is unclear.[3]

Historically, AON has been described as a rare condition diagnosed classically by a characteristic endoscopic appearance of a circumferential black area. The most common primary cause seems to be tissue hypoxia through hypoperfusion from cardiac dysfunction or sepsis. The less vascular lower oesophagus is predictably the most commonly affected site.[13] Other direct causes include severe gastric reflux, viral or fungal infections, allergic reactions to antibiotics, hypothermia or caustic injuries.[14 15] Hyperglycaemic or alcohol intoxication (causing transient gastropathy and malnutrition) have also been implicated as possible mechanisms.[16 17] Seen most commonly in older men with cardiopulmonary comorbidities, the typical presentation is with upper gastrointestinal bleeding.[13 15] Some of the most common risk factors include diabetes mellitus, cardiovascular disease and chronic renal failure.[13 18] Endoscopy reveals diffuse circumferential black discolouration of the oesophagus with sharp demarcation at the Z-line. Histology generally demonstrates necrotic debris, mucosal and submucosal necrosis with local inflammation.[15]

Initial conservative treatment, including hydration, parenteral nutrition, antibiotics, proton pump inhibitors and sucralfate, is typically recommended. In cases with perforation, early surgical or endoscopic interventions have been applied. Common complications include strictures, stenosis, abscesses, tracheoesophageal fistula and perforation. The mortality rate has been reported to be up to 30%, which may also be from underlying comorbidities and risk factors.[15] Mortality directly from the oesophageal disease is reported to be around 6%.[17] Interestingly, the gastrointestinal bleeding caused by AON has not been observed to be significant enough to cause haemodynamic instability.[13]

The cause of the AON in our patient is likely the period of critical illness during his initial hospitalisation as well as the undiagnosed diabetes. It is unclear if there was a direct relationship to SARS-CoV-2, as we could not test the specimen for SARS-CoV-2 RNA. There has been a report of SARS-CoV-2 causing herpetic erosions and ulcers with lymphocytic infiltration in the oesophagus where viral RNA was detected. Similar to our patient, this patient was also an elderly man who presented with ventilator-dependent respiratory insufficiency with resultant gastrointestinal bleeding.[19] The classic endoscopic appearance of a black circumferential area was not present in our case, although there was extensive necrosis extending into the muscularis propria on histology. This is possibly because of the timing of the endoscopy, which occurred approximately a month after discharge from the initial period of illness. A more classic appearance may plausibly have been seen, had he had the endoscopy during the period of initial critical illness.

Given that 19% of patients with SARS-CoV-2 present with severe illness[1] and consequently have some degree of tissue hypoperfusion,[11] AON in such patients may be more frequently seen, specifically as survival rates are expected to increase with newer therapeutic options. With the associated prothrombotic state and frequent anticoagulation, these patients are at an increased risk of gastrointestinal bleeding.[20] It is important for physicians to be aware of AON as an aetiology of gastrointestinal bleeding in these patients. A staging system for AON based on clinical and endoscopic findings[15] may assist in risk stratification and development of evidence-based management guidelines.

Learning points

- Acute oesophageal necrosis (AON) is a rare condition diagnosed classically by a characteristic endoscopic appearance of a circumferential black area. The most common primary cause seems to be tissue hypoxia through hypoperfusion from cardiac dysfunction or sepsis.
- It is estimated that 19% of patients with SARS-CoV-2 are severely ill and may have resulting tissue hypoperfusion which increases their risk of developing AON, especially since survival rates are expected to increase with newer therapeutic options.
- With the associated prothrombotic state and frequent anticoagulation, these patients are at increased risk of gastrointestinal bleeding. It is important for physicians to be aware of AON as an aetiology of gastrointestinal bleeding in these patients.
- A staging system for AON based on clinical and endoscopic findings may assist in risk stratification and development of evidence-based management guidelines.

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