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Severe colon ischemia in patients with severe coronavirus-19 (COVID-19)

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ABSTRACT

COVID-19 is associated with severe coagulopathy. We present three cases of colonic ischemia that can be attributed to the hypercoagulable state related with SARS-CoV2 and disseminated intravascular coagulation.

Three males aged 76, 68 and 56 with respiratory distress presented episodes of rectal bleeding, abdominal distension and signs of peritoneal irritation. Endoscopy (case 1) and computed tomography angiography revealed colonic ischemia. One patient (case 2) in which a computed tomography (CT) scan showed perforation of the gangrenous

cecum underwent surgery. D-dimer levels were markedly increased (2,170, 2,100 and 7,360 ng/ml) in all three patients. All three patients died shortly after diagnosis.

Keywords: COVID-19. Colon ischemia. Colon gangrene. Intravascular disseminated coagulation.

INTRODUCTION

Gastrointestinal symptoms have been reported in between 17.6 % and 35 % of patients with the disease caused by coronavirus SARS-CoV-2 (COVID-19). These include diarrhea (12.5 %), anorexia (78.6 %), nausea and vomiting (10.2 %), abdominal pain (9.2 %) and hematochezia (1.2 %); all are generally associated with respiratory disease or present on their own in 10-15 % of cases (1-3). Raised alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin levels have been reported in 10 %, 21 % and 22 % of cases, respectively (4). The presence of digestive symptoms has been associated with poorer outcome (2).

Several studies have confirmed the tropism of SARS-CoV-2 for the mucosa of the gastrointestinal tract and the presence of viral nucleic acids in the feces in up to 53.4 % of infected patients. Thus suggesting the possibility of fecal-oral transmission (5,6).

METHODS

A total of 827 patients who tested positive for SARS-CoV-2 were treated at our institution from March 4th to April 30th, 2020, of whom 33 patients were admitted to the Intensive Care Unit (ICU). Here we report three patients with severe COVID-19 disease and respiratory failure who received mechanical ventilation and developed a marked increase in D-dimer levels and colonic ischemia (CI). The patients relatives provided consent regarding the publication their data.

RESULTS

Baseline characteristics and laboratory findings are shown in table 1.

Case 1

A 76-year-old male with hypertension was diagnosed with pneumonia due to SARS-CoV-2 based on reverse-transcriptase-polymerase-chain-reaction (RT-PCR) and required mechanical ventilation. He was treated with lopinavir/ritonavir (400 mg/100 mg) twice daily for 14 days, hydroxychloroquine 400 mg for ten days, corticosteroids in a tapering pattern, ceftriaxone and prophylactic anticoagulation with daily low-moderate weight heparin (LMWHs) (7,500 UI).

He experienced several episodes of hematochezia when in ICU. Lower endoscopy showed erythema, edema and fragile mucosa. Computed tomography angiography (CTA) revealed necrotizing pancreatitis and signs of colonic ischemia such as wall thickening, absence of wall enhancement and mesenteric stranding (Fig. 1). Notable analytical findings were high levels of D-dimer of 2,170 ng/ml (normal range 0-229). The patient died 24 hours later.

Case 2

A 68-year-old male with hypertension and type 2 diabetes required mechanical ventilation for bilateral pneumonia caused by SARS-CoV-2 (as diagnosed by RT-PCR). He was treated with lopinavir/ritonavir for eleven days, hydroxychloroquine (400 mg) for eleven days, ciprofloxacin, azithromycin (500 mg/daily) for five days and LWMHs, 7,500 UI.

He developed abdominal distension and paralytic ileus with signs of peritoneal irritation in the ICU. Abdominal CTA revealed perforation of the cecum with pneumatosis of the left colon. A laparotomy was performed which confirmed fecaloid peritonitis, gangrenous perforation of the cecum and diffuse ischemia of the bowel and colon. An ileostomy was performed following peritoneal lavage. The patient died shortly after surgery following 12 days in the ICU.

Case 3

A 56-year-old male with hypertension and type 2 diabetes was diagnosed with pneumonia caused by SARS-CoV-2 (as diagnosed RT-PCR). He suffered respiratory failure, severe systemic inflammatory response syndrome and required mechanical ventilation. He was treated with lopinavir/ritonavir (400 mg/100 mg) twice daily for nine days, hydroxychloroquine (400 mg) for 13 days, levofloxacin and corticosteroids in

a tapering pattern for eight days and LMWHs, 3,500-7,500 UI. In spite of the antithrombotic treatment, he developed segmental pulmonary thromboembolism and pronounced abdominal distension with tenderness and guarding. Abdominal CTA revealed pneumoperitoneum and colonic pneumatosis (Fig. 2). The patient died 24 hours after diagnosis.

DISCUSSION

In the three cases, CI was confirmed by endoscopy, CTA and laparotomy and occlusive arterial ischemia was ruled out as a possible cause. There are several reasons that could explain the ischemic intestinal and colonic damage. Firstly, infection from SARS-CoV-2 in severe cases is characterized by the triggering of a rapid and intense innate immune response (the cytokine storm) associated with the release of proinflammatory and procoagulant cytokines (interleukins, tumor necrosis factor-alfa, interferons) (7). SARs-CoV-2 has a great affinity (ten times greater than SARS-CoV-) for the membrane receptors of the angiotensin-converting enzyme 2 (ACE-2) present in type-II alveolar cells of the lung (AT2), the enterocytes of the ileum and colon and the cholangiocytes and B-cells of the pancreas. This facilitates its entry into cells, its replication and the subsequent cytopathic consequences such as cell death, the release of molecular patterns related to pathogen-associated molecular pattern (PAMPS) and damage-associated molecular patterns (DAMPs). Thus inducing an inflammatory and hemostatic response (8,9). Varga et al. have recently confirmed the presence of viral bodies on endothelial cells and endotheliitis in the small intestine (10).

Given that the intestine is the largest immune organ and expresses abundant ACE-2 receptors for SARS-CoV-2, it is not at all surprising that a severe inflammatory response occurs with damage to the mucosa and necrosis of the intestinal wall. Diffuse damage to the gastrointestinal tract has been observed together with a lymphocytic infiltrate, bleeding and necrosis in rats infected with SARS-CoV and necropsies of COVID-19 patients (11). Furthermore, the systemic inflammatory response and sepsis are associated with thrombotic phenomena and disseminated intravascular coagulation (immunothrombosis) characterized by the massive presence of fibrin deposits, a marked elevation of D-dimer levels and moderately low platelet counts. Recently, Tang has highlighted that most patients that die from COVID-19 develop intravascular

disseminated coagulation and venous thromboembolism (71.6 *vs* 0.6 in survivors) (12). Interestingly, a higher prevalence of deep vein thrombosis has been reported in patients with COVID-19 (13).

Other authors have reported similar phenomena in zoonotic outbreaks involving other viruses. However, it remains unclear if these coagulation disorders are directly induced by SARS-CoV-2 or are secondary to the systemic inflammatory response. Zhangs et al. reported three patients with severe COVID-19 with strokes and phenomena related to peripheral ischemia mediated by antiphospholipid antibodies (14). The association of COVID-19 with venous thromboembolism and occlusive microthrombotic process has led to updates in the clinical guidelines of antithrombotic prophylaxis (15).

Apart from the mechanisms described, non-occlusive mesenteric intestinal ischemia secondary to hypoxemia and low cardiac output cannot be ruled out in patients with severe acute respiratory syndrome (SARS), multiorgan failure and viral sepsis (7). We found eleven cases of mesenteric ischemia and no reports of colon ischemia in disease due to COVID-19 in the review of the literature (Medline with PubMed Interface until June 2020). We are aware of the limitations of the study, such as the fact that a pathologic analysis of the intestine was not available, as necropsy was limited to the thoracic cavity. Currently, only the first reports of the disease caused by COVID-19 are beginning to appear. As the pandemic develops in the near future, more complete data on the pathogenesis of SARS-CoV-2 and its effect on the gastrointestinal tract will become available.

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	Case I	*Case II*	*Case III*
Gender	Male	Male	Male
Age (years)	76	68	56
Comorbidities	Hypertension	Hypertension Type II diabetes Dyslipidemia	Hypertension Type II diabetes COPD Dyslipidemia Obesity (class I)
Days since disease onset	21	13	21
Intensive Care Unit (days)	17	12	21
Days to diagnosis of MI	15	11	19
Complications of Covid-19	Multifocal pneumonia Acute kidney injury (AKIN II) Hematochezia	Bilateral pneumonia *Staphylococcus aureus* pneumonia Paralytic ileus	Multifocal bilateral pneumonia Acute kidney injury (AKIN II) Necrotizing pulmonary Aspergillosis Paralytic ileus Pulmonary embolism
Acute gastro-intestinal symptom	Rectal bleeding	Acute abdomen	Acute abdomen
Vital signs in acute episode			

Blood pressure (mm Hg)		99/41	92/32	115/62
Heart rate (beats per min)		62	60	119
Temperature (°C)		36.9	38.6	38.4
Additional diagnostic tests				
Endoscopy		Ischemic colitis	Pneumoperitoneum	Pneumoperitoneum
CT scan		Ischemic colitis	Bowel perforation	Bowel perforation
		Necrotizing pancreatitis	Pneumatosis intestinalis	Distension of small bowel and right colon
				Pneumatosis intestinalis
				Segmental pulmonary embolism
Laboratory results in acute episode	Reference ranges			
Hemoglobin (g/dl)	*14-17*	9.4	11.4	10.6
White blood cell count (cells x 10^9/l)	*4.8-10.8*	11	15.1	13
Lymphocyte (cells x 10^9/l)	*1.2-4*	0.45	0.42	0.54
Platelets (cells x 10^9/l)	*150-450*	109	269	325
C-reactive protein (mg/dl)	*0.0-0.50*	0.38	31.6	0.1
Procalcitonin (ng/dl)	*0.0-0.50*	0.07	0.9	0.24
D-dimer (ng/ml)	*150-500*	2,170	2,100	7,360
Fibrinogen (mg/dl)	*150-350*	224	886	-

Ferritin(ng/ml)	*30-400*	1,059	1,842	3,665
Lactic acid (mmol/l)	*0.50-2.00*	1.48	1.8	5.69
Lactate deshydrogensase (U/l)	*135-225*	384	348	649
Alanine aminotransferase (U/l)	*0-41*	37	72	108
Aspartate aminotransferase (U/l)	*1-40*	77	24	135
Alkaline phosphatase (U/l)	*40-129*	120	62	57
Gamma glutamyltransferase (U/l)	*0-60*	486	40	136
Ferritin (ng/ml)		1,059		

MI: mesenteric ischemia; AKIN: Acute Kidney Injury Network; COPD: chronic obstructive pulmonary disease; CT: computed tomography.

Figure 1.

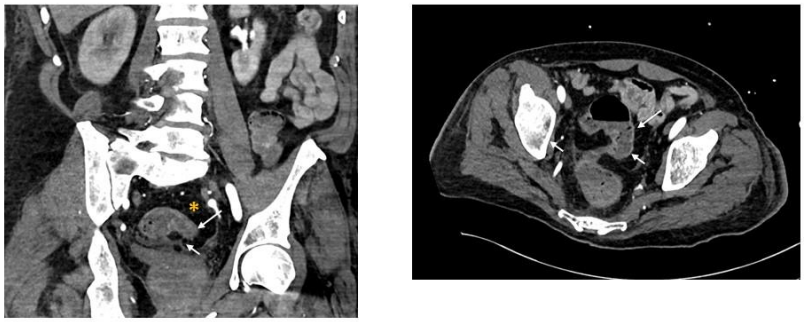

Fig. 1. Case 1. Coronal and axial CT of the pelvis with IV contrast showing wall thickening of the sigma (long arrow), mesenteric stranding (*) and ascites (short arrow).

Figure 2

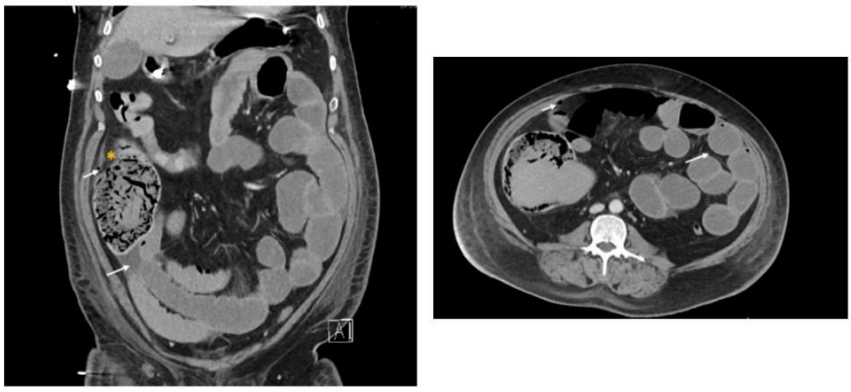

Fig. 2. Case 3. Coronal (A) and axial (B) CT of the abdomen with IV contrast showing small bowel distension and pneumatosis intestinalis (arrow).