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Abstract:	<p>Severe disease caused by the SARS-CoV coronavirus is characterized by patients presenting with respiratory distress associated with a systemic inflammatory response syndrome (cytokine storm). Sixteen to thirty percent of COVID-19 patients also have gastrointestinal symptoms. Here we present three cases of COVID-19 who developed colonic ischemia.</p> <p>Three males aged 76, 68 and 56 with respiratory distress and receiving mechanical ventilation presented episodes of rectal bleeding, abdominal distension and signs of peritoneal irritation. Endoscopy (case 1) and computed tomography angiography revealed colonic ischemia and pneumoperitoneum.</p> <p>One patient (case 2) underwent surgery in which perforation of the gangrenous cecum and colonic ischemia was confirmed.</p> <p>In all three patients D-dimer levels were markedly increased (2170, 2100 and 7360 ng/mL). All three patients died shortly after diagnosis.</p> <p>In severe COVID-19 disease, the pathogenic cause has increasingly become attributed to the development of disseminated intravascular coagulation secondary to the systemic inflammatory response.</p>
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Severe colon ischemia in patients with severe COVID-2019 infection: a report of three cases

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Key Words: COVID-19, colon ischemia, colon gangrene, intravascular disseminated coagulation

ABSTRACT

Severe disease caused by the SARS-CoV coronavirus is characterized by patients presenting with respiratory distress associated with a systemic inflammatory response syndrome (cytokine storm). Sixteen to thirty percent of COVID-19 patients also have gastrointestinal symptoms. Here we present three cases of COVID-19 who developed colonic ischemia.

Three males aged 76, 68 and 56 with respiratory distress and receiving mechanical ventilation presented episodes of rectal bleeding, abdominal distension and signs of peritoneal irritation. Endoscopy (case 1) and computed tomography angiography revealed colonic ischemia and pneumoperitoneum.

One patient (case 2) underwent surgery in which perforation of the gangrenous cecum and colonic ischemia was confirmed.

In all three patients D-dimer levels were markedly increased (2170, 2100 and 7360 ng/mL). All three patients died shortly after diagnosis.

In severe COVID-19 disease, the pathogenic cause has increasingly become attributed to the development of disseminated intravascular coagulation secondary to the systemic inflammatory response.

INTRODUCTION

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

Several studies have confirmed the tropism of SARS-19 for the mucosa of the gastrointestinal tract and the presence of viral nucleic acids in the feces of up to 53.4% of infected patients, thus suggesting the possibility of fecal-oral transmission [4,5].

METHODS

FROM March 4 to April 30, 2020, a total of 33 patients with confirmed COVID-19 were admitted to the intensive care unit (ICU).

Here we report on three patients with severe COVID-19 disease with respiratory failure who received mechanical ventilation and developed a marked increase in D-dimer levels and colonic ischemia (CI). Patients signed informed consent regarding publishing their data.

RESULTS

Baseline characteristics and laboratory findings are shown in Table 1

1 Case 1. A 76-year-old male with hypertension was diagnosed with pneumonia from
2 SARS-CoV-2, based on reverse-transcriptase-polymerase-chain-reaction (RT-PCR) and
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4 required mechanical ventilation. He was treated with lopinavir/ritonavir (400mg/100mg)
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6 twice daily for 14 days, hydroxychloroquine 400 mg for 10 days, corticosteroids in a
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8 tapering pattern, ceftriaxone and prophylactic anticoagulation with daily low-moderate
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10 weight heparin (LMWHs) (7500 UI).
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17 During his ICU stay he experienced several episodes of hematochezia. Lower endoscopy
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19 showed erythema, edema and fragile mucosa. Computed tomography angiography (CTA)
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21 revealed necrotizing pancreatitis and signs of colonic ischemia: wall thickening, absent
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23 of wall enhancement and mesenteric stranding. Notable in the analytical findings were
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25 high levels of D-dimer of 2170 ng/ml (normal range 0-229). The patient died 24 hours
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27 later.
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34 Case 2. A 68-year-old male with hypertension and type 2 diabetes required mechanical
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36 ventilation for bilateral pneumonia caused by SARS-CoV-2 (as diagnosed by RT-PCR).
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38 He was treated with lopinavir/ritonavir for 11 days, hydroxychloroquine (400 mg) for 11
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40 days, ciprofloxacin, azithromycin (500 mg/daily) for 5 days, and LWMHs, 7500 UI.
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46 During his stay in the ICU he developed abdominal distension and paralytic ileus with
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48 signs of peritoneal irritation. Abdominal CTA revealed perforation of the cecum with
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50 pneumatosis of the left colon. A laparotomy was performed which confirmed fecaloid
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52 peritonitis, gangrenous perforation of the cecum and diffuse ischemia of the bowel and
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54 colon. Following peritoneal lavage an ileostomy was performed. The patient died shortly
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56 after surgery following 12 days in the ICU.
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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 from respiratory failure, severe systemic inflammatory response syndrome and required mechanical ventilation. He was treated with lopinavir/ritonavir (400 mg/100 mg) twice daily for 9 days, hydroxychloroquine (400 mg) for 13 days, levofloxacin and corticosteroids in a tapering pattern for 8 days, and LMWHs, 3500-7500 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. The patient died 24 hours after diagnosis.

DISCUSSION

In the three cases described, CI was confirmed by endoscopy, CTA and laparotomy and occlusive arterial ischemia was ruled out as a possible cause. There are several reasons which 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) [6]. SARs-CoV-2 has a great affinity (10 times greater than SARS-CoV-) for the membrane receptors of angiotensin-converting Enzyme 2 (ACE-2) present in type-II alveolar cells of the lung (AT2), the gastric and duodenal mucosa and the enterocytes of the ileum and colon, the cholangiocytes and B-cells of the pancreas thus facilitating its entrance into cells, its replication and the subsequent cytopathic consequences: cell death and release of molecular patterns related to pathogen-associated

1 molecular pattern (PAMPS) and damage-associated molecular patterns (DAMPs),thus
2 inducing an inflammatory and hemostatic response [7,8].
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7 Given that the intestine is the largest immune organ and it expresses abundant ACE-2
8 receptors for SARS-CoV-2, it is not at all strange that a severe inflammatory response
9 occurs with damage to the mucosa and necrosis of the intestinal wall. In rats infected with
10 SARS-CoV and in the necropsies of COVID-19 patients diffuse damage to the
11 gastrointestinal tract has been observed together with a lymphocytic infiltrate, bleeding
12 and necrosis [9].
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24 Furthermore, the systemic inflammatory response and sepsis are associated with
25 thrombotic phenomena and disseminated intravascular coagulation (immunothrombosis)
26 characterized by the massive presence of fibrin deposits, marked elevation of D-dimer
27 levels and moderately low platelet counts. Recently Tang has highlighted that most
28 patients that die from COVID-19 develop intravascular disseminated coagulation and
29 venous thromboembolism (71.6 vs 0.6 in survivors) [10]. Other authors have reported
30 similar phenomena in zoonotic outbreaks involving other viruses. However, it remains
31 unclear if these coagulation disorders are directly induced by SARS-CoV-2 or are
32 secondary to the systemic inflammatory response. Zhangs et al have reported on three
33 patients with severe COVID-19 with strokes and phenomena related to peripheral
34 ischemia mediated by antiphospholipid antibodies [11].
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53 The association of COVID-19 with venous thromboembolism and occlusive
54 microthrombotic process has led to updates in the clinical guidelines of antithrombotic
55 prophylaxis [12]
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1 Apart from the mechanisms described, non-occlusive mesenteric intestinal ischemia
2 cannot be ruled out secondary to hypoxemia and low cardiac output in patients with
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4 severe acute respiratory syndrome (SARS), multiorgan failure and viral sepsis [6].
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9 In the review of the literature (MEDLINE with PubMed Interface, date of last search May
10 2020) we have found no reports of mesenteric and colon ischemia in disease from
11
12 COVID-19. We are aware of the limitations of the study in that pathologic analysis of the
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14 intestine was not available, as necropsy was limited to the thoracic cavity. Currently, only
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16 the first reports of the disease caused by COVID-19 are beginning to appear and as the
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18 pandemic develops in the near future more complete data on the pathogenesis of SARS-
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20 CoV-19 and its effect on the gastrointestinal tract will become available.
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Table 1

	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			
<i>Blood pressure (mm Hg)</i>	99/41	92/32	115/62
<i>Heart rate (beats per min)</i>	62	60	119
<i>Temperature (°C)</i>	36,9	38,6	38,4
Additional diagnostic tests			
<i>Endoscopy</i>	Ischemic colitis		
<i>CT scan</i>	Ischemic colitis	Pneumoperitoneum	Pneumoperitoneum

		Necrotizing pancreatitis	Bowel perforation Pneumatosis intestinalis	Bowel perforation Distension of small bowel and right colon Pneumatosis intestinalis Segmental pulmonary embolism
Laboratory results in acute episode	Reference ranges			
<i>Hemoglobin (g/dl)</i>	<i>14 - 17</i>	9,4	11,4	10,6
<i>White blood cell count (cells x 10⁹/L)</i>	<i>4.8 - 10.8</i>	11	15,1	13
<i>Lymphocyte (cells x 10⁹/L)</i>	<i>1,2 - 4</i>	0,45	0,42	0,54
<i>Platelets (cells x 10⁹/L)</i>	<i>150 - 450</i>	109	269	325
<i>C-reactive protein (mg/dL)</i>	<i>0.0 - 0.50</i>	0,38	31,6	0,1
<i>Procalcitonin (ng/ dL)</i>	<i>0.0 - 0.50</i>	0,07	0,9	0,24
<i>D-dimer (ng/mL)</i>	<i>150 - 500</i>	2170	2100	7360
<i>Fibrinogen (mg/dL)</i>	<i>150 – 350</i>	224	886	-
<i>Ferritin(ng/ml)</i>	<i>30-400</i>	1059	1842	3665
<i>Lactic acid (mmol/L)</i>	<i>0.50 - 2.00</i>	1,48	1,8	5,69
<i>Lactate deshydrogensase (U/L)</i>	<i>135 - 225</i>	384	348	649
<i>Alanine aminotransferase (U/L)</i>	<i>0 - 41</i>	37	72	108
<i>Aspartate aminotransferase (U/L)</i>	<i>1 - 40</i>	77	24	135
<i>Alkaline phosphatase (U/L)</i>	<i>40 - 129</i>	120	62	57
<i>Gamma Glutamyltransferase (U/L)</i>	<i>0 - 60</i>	486	40	136
<i>Ferritin(ng/ml)</i>		1059		

*MI: Mesenteric ischemia; AKIN: Acute Kidney Injury Network; COPD: Chronic Obstructive Pulmonary Disease; CT: computed tomography