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Case Series

Clinical and Intestinal Histopathological Findings in SARS-CoV-2/COVID-19 Patients with Hematochezia

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Keywords

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Abstract

Gastrointestinal (GI) symptoms of SARS-CoV-2/COVID-19 in the form of anorexia, nausea, vomiting, abdominal pain and diarrhea are usually preceded by respiratory manifestations and are associated with a poor prognosis. Hematochezia is an uncommon clinical presentation of COVID-19, and we hypothesize that older patients with significant comorbidities (obesity and cardiovascular) and prolonged hospitalization are susceptible to ischemic injury to the bowel. We reviewed the clinical course, key laboratory data including acute-phase reactants, and drug/medication history in 2 elderly male patients admitted for COVID-19 respiratory failure. Both patients had a complicated clinical course and suffered from hematochezia, acute blood loss, and anemia which led to hemodynamic instability requiring blood transfusion around day 40 of their hospitalization. Colonoscopic impressions were correlated with the

histopathological findings in the colonic biopsies that included changes compatible with ischemia and nonspecific acute inflammation, edema, and increased eosinophils in the lamina propria. Both patients were hemodynamically stable, on prophylactic anticoagulants, multiple antibiotics, and antifungal agents due to respiratory infections at the time of lower GI bleeding. Hematochezia resolved spontaneously with supportive care. Both patients eventually recovered and were discharged. Elderly patients with significant comorbid conditions are uniquely at risk for ischemic injury to the bowel. This case report highlights hematochezia as an uncommon GI manifestation of spectrum of COVID-19 complications. The causes of bleeding in these COVID-19 associated cases are likely multifactorial and can be attributed to concomitant etiologies based on their age, multiple comorbid conditions, prolonged hospitalization compounded by lung injury, and hypoxia precipitated by the virus. We hypothesize that rather than a direct viral cytopathic effect, ischemia and hypoperfusion may be unleashed due to the cytokine storm orchestrated by the virus that leads to abnormal coagulation profile. Additional factors that may contribute to ischemic injury are prophylactic use of anticoagulants and polypharmacy. There were no other causes to explain the brisk lower GI bleeding. Presentation of hematochezia was followed by hemodynamic instability that may further increase the mortality and morbidity of COVID-19 patients, and prompt consultation and management by gastroenterology is therefore warranted.

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Introduction

In January 2020, molecular-based studies identified the infectious agent SARS-CoV-2/COVID-19 (novel coronavirus 2019) from a cluster of cases of pneumonia reported in December from Wuhan, Hubei Province, China [1], which has caused a worldwide pandemic. The viral infection typically manifests initially by cough and fever that rapidly escalates to pneumonia and respiratory failure in some patients [2] leading to increased morbidity and mortality, especially in the older population (>75 years old) [3]. Gastrointestinal (GI) symptoms usually present as anorexia, nausea, vomiting, abdominal pain, anosmia, hypogeusia, and diarrhea. These symptoms are usually associated with poor prognosis [4]. The possibility of fecal-oral transmission is also supported by the fact that the virus can be identified in the stool and rectal swabs of infected patients even with a negative nasopharyngeal swab test [5, 6]. It has also been shown that SARS-CoV-2 uses angiotensin-converting enzyme (ACE2) as a viral receptor for the entry process [7]. By using quantitative polymerase chain reaction, researchers have shown that high levels of ACE2 mRNA expression can be detected in the GI tract especially in the small bowel and in the colon providing the likely route for viral infection [7]. In this report, we present the clinical course, colonoscopy findings correlated with the corresponding histopathological changes, and pertinent laboratory findings in 2 patients with SARS-CoV-2/COVID-19 pneumonia, complicated by an uncommon presentation of hematochezia, attributed to multifactorial etiological causes during their prolonged hospitalization.

Case Report/Case Presentation

Clinical History and Hospital Course for Case 1

A 67-year-old man with a past medical history of obesity (108.9 kg, body mass index 38.45 kg/m²), diabetes mellitus type 2, hypertension, hyperlipidemia, and left bundle branch block presented to the emergency department with fever and chills for 8 days and cough with shortness of breath for 3 days. The patient received hydroxychloroquine from his primary care provider for presumed COVID-19 infection, but it was discontinued by the patient after two doses. The patient and family were unable to recall the exact dose of the prescribed medication. On admission, his nasopharyngeal swab was positive for SARS-CoV-2 virus. The patient's COVID-19 pneumonia was complicated by acute hypoxic respiratory failure requiring intubation. His nasal swab was also positive for methicillin-susceptible *Staphylococcus aureus*.

The patient's hospital course was further complicated by a non-ST elevation myocardial infarction, atrial fibrillation with rapid ventricular rate, diabetes insipidus, toxic encephalopathy, acute kidney injury, and right upper and lower extremity weakness. He also developed acute occlusive deep vein thrombosis of his right peroneal vein for which he received apixaban. His medications included azithromycin (500 mg, oral daily, 5 doses), hydroxychloroquine (400 mg, oral, 2 times daily, 2 doses followed by 200 mg, oral, 2 times daily, 8 doses), ceftriaxone, fluconazole, vancomycin, piperacillin/tazobactam, and cefazolin. Aminoglycosides were not used for Gram-negative infection.

On day 33 of hospitalization, the patient had several episodes of frank red blood with clots per rectum coupled with hemodynamic instability. His blood pressure prior to hematochezia varied from 138 to 127/79 to 73 mm Hg and dropped to 87–76/55–40 mm Hg after the bleeding episode, requiring blood transfusion. Possible etiologies for hematochezia were clinically determined to be lower GI including rectal ulcer from flexi-seal, hemorrhoids, arteriovenous malformation (AVM), diverticulosis, and malignancy. Prior surveillance colonoscopies were unavailable for comparison. Upper endoscopy was not performed due to low clinical index of suspicion for rapid upper versus lower GI bleeding source. In addition, given the COVID-positive status of the patient and interim guidelines issued jointly by GI societies (AASLD, ACG, AGA, and ASGE) that endoscopic procedures themselves could potentially result in a virus super-spreading event, only emergent diagnostic colonoscopy was performed to identify the source of bleeding. CT enterography was used to rule out small bowel pathology. At the time of GI bleeding, the patient was on pantoprazole, albuterol, aspirin (low dose), fluconazole for candidemia (*Candida tropicalis*), furosemide, oxycodone, and piperacillin-tazobactam. Anticoagulation for DVT was stopped temporarily in the setting of active bleeding.

Colonoscopy Findings

Notable findings included a few scattered non-bleeding erosions and shallow ulcerations in the transverse colon, hepatic flexure, and ascending colon (shown in Fig. 1a). Biopsies of the ulcerated mucosa and of normal mucosa were obtained. The terminal ileum appeared normal. The source of hematochezia was considered to be from the small scattered proximal colonic erosions and shallow ulcers, exacerbated by the patient's use of apixaban. No other

probable source of bleeding in the form of hemorrhoids, AVM), diverticulitis and/or malignancy was identified. Prior surveillance colonoscopies were not available for comparison.

Histopathological Findings

The colonic mucosa featured an erosion, withered crypts, and nonspecific acute inflammation (shown in Fig. 1b). The overall findings were consistent with an ischemic pattern of injury. Alternate possibilities of infection and drug/medication-mediated mucosal injury were raised. No specific features of chronicity were identified. No viral cytopathic changes or microthrombi were seen. An immunohistochemical stain for cytomegalovirus was negative.

Outcome

On day 18, the patient had a tracheostomy placement and was decannulated on day 35. GI bleeding resolved spontaneously after a day (day 34), and anticoagulation was resumed without any further complications. The patient continued to improve clinically, and the nasopharyngeal swab was negative for SARS-CoV-2 virus on days 40 and 42. The patient was discharged home with rehabilitation on day 49 and continues to be followed up as an outpatient.

Clinical History and Hospital Course for Case 2

A 68-year-old man with a past medical history of tobacco use, obesity (81.6 kg body weight, 29 kg/m² BMI), diabetes mellitus 2, hypertension, hyperlipidemia, and coronary artery disease was brought to the emergency department for cough, fever, loose stools, and altered mental status for 5 days. On admission, nasopharyngeal swab was positive for SARS-CoV-2 virus by PCR. COVID-19 pneumonia was complicated by acute hypoxic respiratory failure requiring intubation. His clinical course was complicated by sepsis, acute kidney injury requiring peritoneal dialysis, ileus, toxic metabolic encephalopathy, and candidemia (*Candida tropicalis* and *Candida glabrata*). On day 40 of his hospitalization, intermittent hematochezia requiring blood transfusion was noted. His blood pressure prior to hematochezia varied from 138 to 175/69 to 80 mm Hg and dropped to 118/49 mm Hg after passing large clots and liquid dark and bright red blood. A subset of his critical laboratory parameters is highlighted in Table 2. CT of the abdomen and pelvis showed the bowel was of normal caliber with no evidence of obstruction. Colonoscopy was performed to identify the source of bleeding. Medications included azithromycin (500 mg, oral daily, 5 doses), hydroxychloroquine (400 mg, oral, 2 times daily, 2 doses followed by 200 mg, oral, 2 times daily, 8 doses). At the time of the bleeding, the patient was being treated with fluconazole, meropenem, micafungin, intravenous vancomycin, and ampicillin-sulbactam. Stool culture was negative for cysts, ova, and parasites.

Colonoscopy Finding

Patchy, deeply ulcerated mucosa with significant edema and decreased vascular pattern was present in the cecum with involvement of the ileocecal valve (shown in Fig. 1c). There was diffuse oozing of the mucosa, and the endoscopic appearance of the mucosa was clinically consistent with ischemic colitis. The ileocecal valve showed significant edema and ulceration. Biopsies were taken with cold forceps for histological evaluation. Normal mucosa was found in the remaining portions of the colon. Similar to the findings for case 1, no evidence of

hemorrhoidal bleeding, AVM, diverticulitis, and/or malignancy was noted. Prior colonoscopies were not available for comparison.

Histopathological Findings

The cecal mucosa showed focal edema, mildly active nonspecific inflammation, and focal increased eosinophils in the lamina propria. There was no definitive evidence of ischemia (shown in Fig. 1d). No viral cytopathic effects for CMV or HSV were seen; hence, immunohistochemical stains were not undertaken. Serological tests for CMV were negative. There were no histopathological features suggestive of eosinophilic colitis. The mildly increased eosinophils in the lamina propria were interpreted to be nonspecific. Clinical and histopathological evidence for chronic idiopathic inflammatory bowel disease, scleroderma, and Churg-Strauss syndrome were lacking.

Clinical Outcome

GI bleeding resolved spontaneously. Patient's nasopharyngeal swab was negative for SARS-CoV-2 virus (day 44). He was decannulated on day 54 and was admitted to rehabilitation unit on day 58. Currently, the patient is being followed up in the outpatient clinic.

Discussion/Conclusion

GI manifestations of COVID-19 are seen more often than originally suspected in COVID-19 patients [8–10]. The cases presented are male patients above 65 years of age with complicated and prolonged hospitalizations. Both patients presented with severe COVID-19 pneumonia resulting in hypoxic and respiratory failure on arrival, and only one of them (case 2) presented with GI symptoms in the form of loose stools. Both patients were obese and had cardiac comorbidities that are known to increase the morbidity and mortality in such cases [11]. The hospital courses for both patients were remarkable for lower GI bleeding in the latter part (>40 days) of hospitalization. Colonoscopies were remarkable for scattered erosions and ulceration clinically compatible with ischemia. Upper GI bleeding was excluded clinically, and endoscopies were not performed in order to prevent super-spreader event as per hospital and GI society guidelines. The histopathological findings of the GI tract showed ischemic pattern of injury in case 1 confirming the clinical and endoscopic findings of ischemic colitis. Ischemic injury to the bowel manifests histopathologically as patchy changes. It is likely that the biopsies from case 2 that featured mildly active nonspecific colitis, reactive changes with mild nonspecific increase in lamina propria eosinophils could have been taken from an area of colonic mucosa in transition to overt ischemia. There were no features of chronicity in both cases and other causes of increased eosinophils in the lamina propria were ruled out. Both patients were hemodynamically stable and not on any vasopressors prior to the onset of hematochezia. The patients were however on multiple medications, including anticoagulants, antibiotics, and antifungal agents at the time of hematochezia. Lower GI bleeding is an uncommon manifestation of COVID-19 and has been recently reported as a presenting symptom in an elderly male [12]. It is unclear if the GI symptoms of COVID-19 infection are caused by thrombosis due to altered

coagulation profile (shown in [Table 1](#) and [Table 2](#)) or as a consequence of tissue damage secondary to an immunologically mediated cytokine storm, rather than a direct interaction of these epithelial cells with the virus [13]. Additionally, an abnormal coagulation profile featuring significantly elevated D-dimer, fibrin degradation product levels, increased prothrombin time, and activated partial thromboplastin time has also been reported in COVID-19 patients [14] and was also seen in our patients.

To our knowledge, this is the first histopathological and clinical correlation from colonic biopsies of 2 patients with severe COVID-19 pneumonia complicated by hematochezia during the later phase of their prolonged hospitalizations [15]. Potential etiologies for the colonoscopic and histopathological findings may include thromboembolic events, specifically formation of microthrombi, that may be evident in resection and autopsy specimens rather than biopsy samples. Other possible etiologies include tissue damage caused directly by the viral cytopathic effect, the cytokine storm, or a drug-induced injury. Careful review of medications, management of coagulation profile, and early consultation with gastroenterology are warranted to improve morbidity and mortality outcomes.

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Statement of Ethics

Every precaution has been taken to protect the privacy of research subjects and the confidentiality of their personal information. The study protocol was approved by the institute's committee on human research. All patients in this report are identified by numbers. All necessary patient/participant consent has been obtained and covered by institution's universal consent policy. The study was approved by IRB protocol from NYU Grossman School of Medicine, Protocol Number S20-00528.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.C., W.L. interpreted histopathology. S.B. performed colonoscopies on both cases and provided interpretation of clinical data. D.H., W.L., S.A.S. contributed to acquisition of micrographs. M.C., W.L., S.B., D.H., Y.S., N.D.T. and W.C. interpreted data, edited manuscript, provided intellectual input. S.A.S., M.C. and W.L. reviewed chart. S.A.S. wrote the IRB and manuscript.

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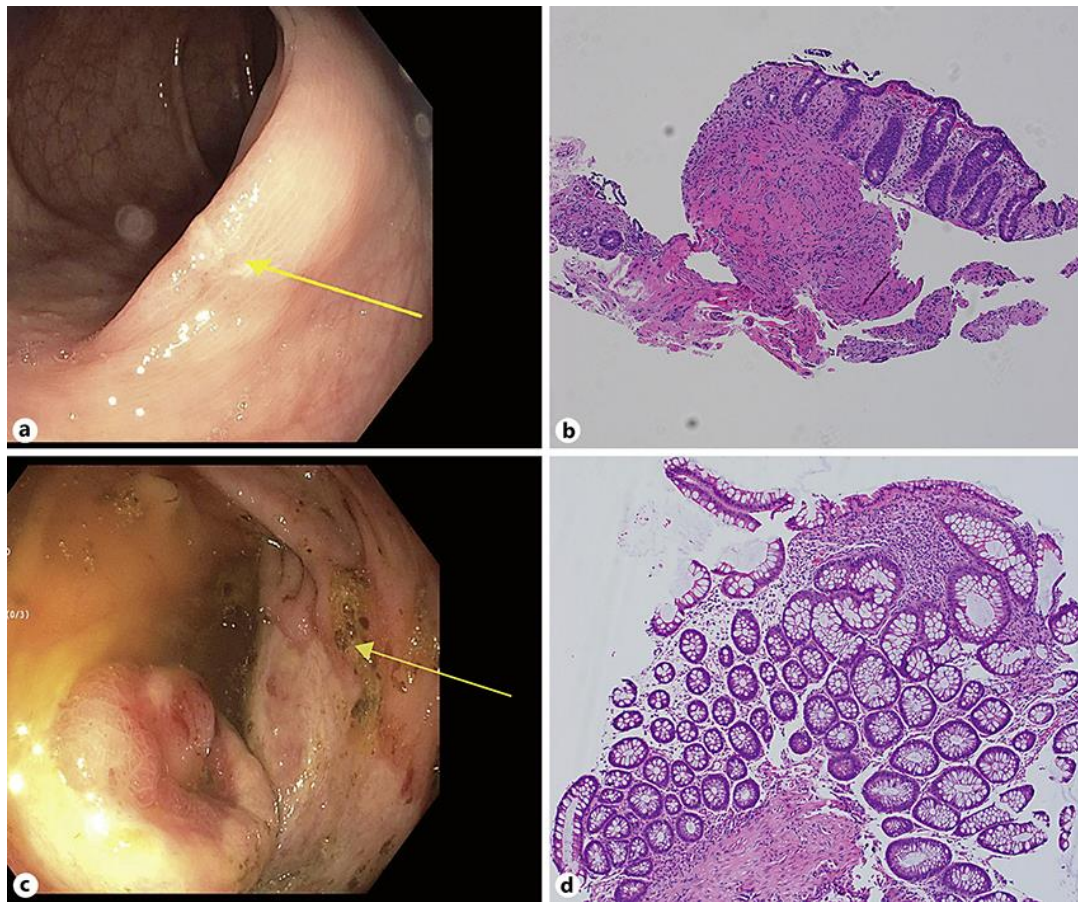


Fig. 1. Colonoscopic findings (a, c) and histopathology of biopsies (b, d) counterstained with hematoxylin and eosin ($\times 100$). **a** Case 1, transverse colon with erosion (yellow arrow). **b** Case 1, colonic mucosa with erosion, withered crypts, and nonspecific acute inflammation, consistent with ischemic pattern of injury. **c** Case 2, ileocecal valve with erosions (yellow arrow). **d** Ileocolic mucosa with edema, mildly active nonspecific inflammation, and focally increased eosinophils in the lamina propria.

Table 1. Pertinent laboratory findings from case 1

	Admission (day 1)	Peak	Discharge (day 49)
Cobas SARS-CoV-2 real time RT-PCR	Detected	N/A	Not detected (retested on day 40 and 42)
Hemoglobin	13.9 g/dL	6.7 g/dL (day 4,041) Intermittent rectal bleeding (day 33)	9.0 g/dL
WBC	$9.7 \times 10^3/\mu\text{L}$	$28.4 \times 10^3/\mu\text{L}$	$5.4 \times 10^3/\mu\text{L}$
D-dimer	284 ng/mL DDU	3,414 ng/mL DDU (day 24)	375 ng/mL DDU
Lactate dehydrogenase	398 U/L	463 U/L (day 11)	264 U/L
Procalcitonin	0.13 ng/mL	0.75 ng/mL (day 35)	0.08 ng/mL
C-reactive protein	154.4 mg/L	163.6 mg/L (day 2)	23.5 mg/L
AST	56 U/L	461 U/L (day 18)	108 U/L
ALT	49 U/L	629 U/L (day 18)	198 U/L
Alkaline phosphatase	44 U/L	1521 U/L (day 40)	1,370 U/L
Bilirubin direct	0.3 mg/dL	0.7 mg/dL (day 18)	0.4 mg/dL
Creatinine	0.82 mg/dL	5.15 mg/dL (day 13)	0.62 mg/dL
Blood glucose	101 mg/dL	367 mg/dL (day 10)	175 mg/dL

Table 2. Pertinent laboratory findings from case 2

	Admission (day 1)	Peak	Discharge to rehabilitation (day 58)
Cobas SARS-CoV-2 real time RT-PCR	Detected Detected again day 43	N/A	Not detected (day 44)
Hemoglobin	12.8 g/dL	6.83 g/dL (day 41 *Colonoscopy (day 40)	8.04 g/ dL (day 53)
WBC	$5.5 \times 10^3 / \mu\text{L}$	$26.2 \times 10^3 / \mu\text{L}$ (day 12) (day 12)	$9.1 \times 10^3 / \mu\text{L}$ (day 53)
D-dimer	456 ng/mL DDU	4,536 ng/mL DDU (day 12)	555 ng/ml DDU (day 53)
Lactate dehydrogenase	273 U/L	1,134 U/L (day 11)	336 U/L
Procalcitonin	0.14 ng/mL	7.59 ng/mL (day 14)	0.45 ng/dL (day 34)
C-reactive protein	150.3 mg/L	382.4 mg/L (day 3)	50.8 mg/L (day 50)
AST	25 U/L	420 U/L (day 12) day 12)	40 U/L (day 51)
ALT	49 U/L	629 U/L (day 1,812)	198 U/L (day 51)
Alkaline phosphatase	47 U/L	695 U/L (day 47)	570 U/L (day 51)
Bilirubin direct	0.3 mg/dL	0.4 mg/dL (day 18)	0.2 mg/dL
Creatinine	1.06 mg/dL	7.66 mg/dL (day 13)	1.65 mg/dL
Blood glucose	181 mg/dL	414 mg/dL (day 12)	160 mg/dL