

Case Report: Ischemic Enterocolitis Associated with Coronavirus Disease 2019: Two Case Reports and a Review of the Literature

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Abstract. The COVID-19 pandemic has caused serious health and social concerns worldwide. Although the primary target of SARS-CoV-2 is the respiratory tract, SARS-CoV-2 infection also causes extrapulmonary symptoms. Previous articles have reported ischemic colitis in COVID-19 patients; however, information regarding its clinical manifestations and pathophysiology is limited. In this case report, we present two cases of ischemic enterocolitis in COVID-19 patients and review past case reports. Our literature review has shown that computed tomography rather than endoscopy was used for the diagnosis, and any region of the intestine was affected. Because the elevation of the D-dimer, which suggested a hypercoagulable state, was reported in most cases, we assumed that thrombosis at any level in the artery and vein was involved in the pathophysiology of COVID-19-associated enterocolitis. SARS-CoV-2-induced endotheliitis can cause both coarctation of the vessels and thrombosis; therefore, both patterns of ischemic colitis, occlusive and nonocclusive, may be involved in COVID-19-associated enterocolitis.

INTRODUCTION

COVID-19, first identified in Wuhan, China, in December 2019, is the cause of an ongoing pandemic. Although the main manifestation of COVID-19 is respiratory infection, extrapulmonary symptoms, such as cerebral infarction, can occur.¹ In addition, Pan et al.² reported that 51% of COVID-19 cases had gastrointestinal symptoms such as loss of appetite, diarrhea, and vomiting. Recently, some articles have demonstrated ischemic colitis in COVID-19 patients;^{3–9} however, information on its clinical manifestations and pathophysiology is limited. Herein, we report two cases of COVID-19-associated ischemic enterocolitis and review past case reports.

CASE REPORTS

Case 1. A 45-year-old previously healthy man visited a community hospital complaining of fever and dyspnea. The real-time PCR (QuantiTect Probe RT-PCR Kit, QIAGEN, Hilden, Germany) performed using the nasal swab was positive for SARS-CoV-2. His respiratory condition worsened, despite treatment with favipiravir. Thereafter, he was transferred to our hospital. He was intubated on day 3 of admission, and extracorporeal membrane oxygenation (ECMO) was initiated on day 5. Together with ECMO therapy, unfractionated heparin was administered continuously. His condition gradually improved; ECMO was terminated on day 14, and he was weaned from ventilatory support on day 17. However, he experienced hematochezia on day 18. Fecal cultures did not indicate the presence of pathological bacteria, and the tests for the *Clostridioides difficile* toxins A/B were

negative. In addition, the cytomegalovirus pp65 antigenemia assay was negative. Although endoscopy was abandoned, we suggested a diagnosis of ischemic enterocolitis owing to a persistent elevated D-dimer level (12.5 µg/mL on day 18); unfractionated heparin administration was continued. Enhanced computed tomography (CT) on day 25 revealed no evidence of intravascular thrombi but showed layered thickening of the descending colon and engorgement of the mesenteric vessels, suggesting ischemic colitis (Figure 1). In addition, a thrombus in the left internal jugular vein, where the cannula was inserted during the ECMO therapy, was seen. Hematochezia improved upon the termination of tube feeding. The patient was switched from unfractionated heparin to an oral anticoagulant on day 33; he was discharged on day 38. The use of the oral anticoagulant was continued for 6 months.

Case 2. A 68-year-old woman visited our hospital with a 2-day history of intermittent left dorsal pain and fever. She had been hospitalized for COVID-19 pneumonia and was discharged with full recovery, 23 days previously. Abdominal CT on day 4 of this hospitalization revealed no evidence of intravascular thrombi but showed marked thickening with a target sign in the upper jejunum (Figure 2). The distribution of the lesion was segmental. The patient had not developed diarrhea during hospitalization, which suggested that infectious enterocolitis was not likely. Although she denied having melena, her blood hemoglobin had decreased from 11.4 g/dL (on the day of this admission) to 8.5 g/dL (on day 9); it increased to 9.9 g/dL after discharge. During her previous hospital admission, her blood D-dimer level elevated to 23.7 µg/mL but decreased by 7.2 µg/mL at discharge. During this hospitalization, it reascended from 1.1 (day 1) to 4.5 µg/mL (day 12), indicating a hypercoagulable state. Taken together, we diagnosed ischemic jejunitis associated with COVID-19. Her symptoms improved with conservative therapy such as bowel rest and pain killers. She was discharged on day 15.

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FIGURE 1. Coronal computed tomography (CT) scan of case 1. Enhanced CT scan on day 25 revealing a layered thickening of the descending colon (arrows) and engorgement of the mesenteric vessels.

DISCUSSION

SARS-CoV-2 infects host cells via the angiotensin-converting enzyme 2 expressed on type II alveolar cells and others, including endothelial cells.¹⁰ Systemic inflammation and diffuse endotheliitis by SARS-CoV-2 can induce a hypercoagulable state, resulting in arterial and venous thromboembolism.^{11,12} We



FIGURE 2. Coronal computed tomography (CT) scan of case 2. Enhanced CT scan on day 4 revealing a marked thickening with a target sign in the upper jejunum (arrows). The lesion is distributed segmentally, suggesting an ischemic rather than an infectious enterocolitis.

reviewed past case reports in which COVID-19 patients, including our cases, presented with ischemic enterocolitis. These are shown in Table 1. CT was used for the diagnosis because endoscopy was abandoned in most cases. Endoscopy is an important tool for the diagnosis of gastrointestinal (GI) diseases, including ischemic enterocolitis. However, in a realistic medical setting, the procedure is often abandoned in patients with COVID-19 because of a lack of personal protective equipment and the possible risk of SARS-CoV-2 transmission to health-care workers. In terms of the sites of lesions in the past reports, any region of the intestine was affected.

Since the elevation of the D-dimer, which suggested a hypercoagulable state was reported in most cases, we assumed that thrombosis at any level in the artery and vein was involved in the pathophysiology of COVID-19-associated enterocolitis. Ischemic colitis is commonly categorized into two classical patterns, occlusive and nonocclusive. However, it is difficult to categorize COVID-19-associated ischemic enterocolitis into these two patterns because its pathophysiological mechanism is not fully understood. In fact, thrombi were observed during pathological examinations in cases where thrombi were not seen in CTs.^{5,7} We assumed that SARS-CoV-2-induced endotheliitis can cause both coarctation of the vessels and thrombosis; therefore, both patterns of ischemic colitis, occlusive and nonocclusive, may be involved in COVID-19-associated enterocolitis.

In conclusion, our presentation of two cases of ischemic colitis in COVID-19 patients has indicated that we should be aware of systemic thrombotic complications, including ischemic enterocolitis, due to SARS-CoV-2 infection, as well as pulmonary manifestations. In addition, when developing their therapeutic strategies, physicians should consider COVID-19-related hypercoagulability when patients with COVID-19 experience GI bleeding. Because information regarding COVID-19-associated ischemic colitis is limited, the accumulation of more case reports and further research are needed to understand the pathophysiology.

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TABLE 1
Past case reports of COVID-19 patients who presented with ischemic enterocolitis

Age, gender	Underlying diseases	GI symptoms	Diagnostics	Site of lesion	Intestinal findings	Thrombi in GI vessels	D-dimer (ng/mL)*	Treatment	Outcome	References
73, Male	HTN, end-stage chronic kidney disease	Abdominal pain, bloody diarrhea	CT	Sigmoid colon	Mucosal hyperenhancement with mass-like thickening	ND	4,226	Anticoagulation	Dead	Chan et al. ³
76, Male	HTN	Hematochezia	Endoscopy, CT	Sigmoid colon	Wall thickening, absence of wall enhancement, mesenteric stranding	NM	2,170	Anticoagulation	Dead	Almeida et al. ⁴
68, Male	HTN, DM, dyslipidemia	Abdominal distension, paralytic ileus	CT	Cecum, colon	Perforation of the cecum with pneumatosis of the descending colon	NM	2,100	Surgical resection	Dead	Almeida et al. ⁴
56, Male	HTN, DM, chronic obstructive pulmonary disease, dyslipidemia	Abdominal pain, guarding	CT	Small intestine, colon	Pneumoperitoneum, colonic pneumatosis	NM	7,360	Anticoagulation	Dead	Almeida et al. ⁴
82, Female	HTN, DM	Abdominal distension and pain	CT	Cecum, ascending colon	Pneumatosis	Microvascular thrombus (pathology)	1,300	Surgical resection, anticoagulation	Alive	Singh et al. ⁵
66, Male	None	Melena, multiple ulceration in the sigmoid colon	Endoscopy	Sigmoid colon	Large clots with multiple ulcerations	NM	NM	Conservative therapy	Alive	Paul et al. ⁶
53, Male	DM, dyslipidemia	Abdominal pain, vomiting	CT	Ascending colon	Mucosal hypo-enhancement	Mesenteric venous thrombus (pathology)	NM	Anticoagulation	Alive	Gonzalez et al. ⁷
52, Male	None	Abdominal pain, vomiting, diarrhea	CT	Intestine (location not specified)	Bowel distension	Superior mesenteric arterial thrombus	NM	Surgical resection	Alive	Beccara et al. ⁸
45, Male	Vitiligo	Abdominal pain, nausea	CT	Ileum, cecum	Ischemic changes in the distal ileum and the cecum	Superior mesenteric arterial thrombus	1,450	Surgical resection	Alive	Rodriguez-Nakamura et al. ⁹
42, Female	Obesity (body mass index: 62), ventriculoperitoneal shunt	Abdominal pain, rectorrhagia	CT	Jejunum	Abdominopelvic collection containing gas in the mesentery	Portal and mesenteric venous thrombus	14,407	Surgical resection	Dead	Rodriguez-Nakamura et al. ⁹
45, Male	None	Hematochezia	CT	Descending colon	Layered thickening of the descending colon and engorgement of the mesenteric vessels	ND	12,500	Anticoagulation	Alive	Case 1
68, Female	Cervical spondylosis myelopathy	Left dorsal pain, fever	CT	Upper jejunum	Marked thickening with target sign (segmental lesion)	ND	1,100	Conservative therapy	Alive	Case 2

CT = computed tomography; DM = diabetes mellitus; GI = gastrointestinal; HTN = hypertension; ND = not detected; NM = not mentioned.

*Reference range: 0–500 ng/mL.

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