SARS-CoV-2 Gastrointestinal Infection Causing Hemorrhagic Colitis: Implications for Detection and Transmission of COVID-19 Disease

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INTRODUCTION

The betacoronavirus, SARS-CoV-2, that is responsible for COVID-19 disease and that was first described in Wuhan, China in late 2019, has swiftly made its way around our world, resulting in excess of 30,000 deaths to date (1). Efforts to recognize SARS-CoV-2 infection have focused on respiratory symptoms such as cough and shortness of breath (2, 3). Currently, the Centers for Disease Control and Prevention (CDC) criteria for identifying persons under investigation (PUI) for SARS-CoV-2 infection in the United States comprise respiratory symptoms and/or fever only (5).

Recent reports from China have described concomitant digestive symptoms, such as nausea, vomiting, diarrhea, and abdominal pain, in patients with confirmed SARS-CoV-2 pulmonary infection (6, 7, 8, 9, 10) and the presence of SARS-CoV-2 RNA in fecal samples (9, 11). However, it remains unclear whether these digestive symptoms were causally related to SARS-CoV-2 gastrointestinal infection. Because the main goals of the care in these cases were to treat the pulmonary disease and limit healthcare worker exposure, a comprehensive evaluation of the gastrointestinal system to implicate the virus and rule out alternative etiologies was not undertaken.

We present a case of SARS-CoV-2 gastrointestinal infection causing acute hemorrhagic colitis and signaling COVID-19 disease which endoscopy confirmed colonic injury and helped exclude other etiologies of disease. We believe that this observation has important implications for the ongoing management and prevention of COVID-19 disease.

CASE REPORT

A 71-year-old woman with a history of hypertension, depression, and chronic back pain, had returned to the United States in early March 2020 following a 10-day trip to Egypt which included a 4-day cruise on the Nile River. On her last day in Egypt, she developed diffuse

abdominal pain and non-bloody diarrhea. The next day, while traveling back to the United States, her diarrhea became bloody. Over the next 4 days she experienced nausea, vomiting, anorexia, diffuse abdominal pain and distention, and 10-20 bloody bowel movements daily.

She presented to our emergency department 5 days following the onset of her symptoms. Physical examination revealed a temperature of 36.4°C (97.6°F), blood pressure of 140/81 mm Hg, pulse of 98 beats per minute, respiratory rate of 18 breaths per minute, and oxygen saturation of 99% on ambient air. Lung auscultation was normal. Abdominal examination demonstrated normal bowel sounds and diffuse tenderness to palpation, but no signs of peritonitis. Red blood, mixed with loose stool, was present in her bedside commode. On further questioning, she denied fever, cough, shortness of breath, sore throat, or any other symptoms. She also denied a personal and family history of gastrointestinal disease and had undergone a normal screening colonoscopy one month prior. She denied antibiotic, antidiarrheal, and non-steroidal anti-inflammatory use, food allergies, lactose intolerance, alcohol abuse, smoking, and drug use. Her medications did include llisinopril, as well as desvenlafaxine, amlodipine, and as-needed morphine for chronic back pain. She reported having been vaccinated against Hepatitis A, B, and typhoid before her trip to Egypt.

Laboratory evaluation was notable for an elevated white blood cell count of 24.4 K/µL, with 20.8 K/µL neutrophils and normal lymphocyte and eosinophil distributions, a normal hemoglobin, and slightly elevated creatinine at 1.31 mg/dL (baseline 0.90 mg/dL). CT scan of her abdomen and pelvis with intravenous contrast showed severe colonic inflammation that was most pronounced in the ascending, transverse, and descending colon, but was also apparent in the sigmoid colon (Figure 1). There was also a small, right pleural effusion.

Given the presumptive diagnosis of traveler's diarrhea with dysentery, empiric ceftriaxone, azithromycin, and metronidazole were initiated intravenously. Before administration of antimicrobials, a fecal sample was obtained and was negative for fecal leukocytes, stool culture (*Campylobacter*, *Salmonella*, *Shigella*, Shiga-toxin producing *E. coli*, and *Yersinia*), ova and parasites, and *Clostridium difficile* toxin (GDH Antigen-toxin screen). The next day, another fecal sample was negative for *Entamoeba histolytica* antigen and *Giardia* antigen. Of note, later in the hospitalization (hospital day 7), fecal molecular testing (FilmArray; BioFire Diagnostics, Salt Lake City, UT) was also negative for bacterial, viral, and parasitic pathogens. HIV 1, 2 antibodies and *Legionella* urine antigen were also negative.

Over the next 3 days, the patient's abdominal pain and bloody diarrhea persisted despite antimicrobial support. Given a concern for inflammatory bowel disease, a C-reactive protein on hospital day 3 was 11.6 mg/dL. Also on hospital day 3, the patient learned that someone in her travel group had been diagnosed with SARS-CoV-2 pulmonary infection. The patient was then immediately moved to a negative-pressure room and SARS-CoV-2 precautions were instituted. On hospital day 4, nine days following the onset of her digestive symptoms, the patient

developed a cough; nasopharyngeal swabs were sent for comprehensive viral detection, including SARS-CoV-2 RNA (Quest Diagnostics).

Given the patient's elevated C-reactive protein and persistent abdominal pain and bloody diarrhea, a flexible sigmoidoscopy was performed on hospital day 4 to evaluate for evidence of inflammatory bowel disease or ischemic colitis. Endoscopic evaluation to 40 cm from the anal verge revealed patchy areas of focal erythema without ulceration in the descending colon, sigmoid colon, and rectum (Figure 2). Histological examination of the colon and rectal biopsies by hematoxylin and eosin stain under light microscopy showed slight expansion of the lamina propria by edema with normal cellularity and intact crypts. No virocytes or protozoa were seen. There were no microscopic changes to indicate the presence of classic infectious colitis, ischemia, or inflammatory bowel disease.

On the evening of hospital day 4, the patient's nasopharyngeal swab for comprehensive respiratory viral panel returned positive for rhinovirus and herpes simplex virus 1. Her SARS-CoV-2 RNA was also positive by reverse-transcriptase-polymerase-chain-reaction (rRT-PCR). Over the next several days, the patient's abdominal pain and bloody diarrhea persisted, and a sore throat developed. On hospital day 7, a SARS-CoV-2 rRT-PCR performed on a fecal sample using the swab and viral transport media from a SARS-CoV-2 nasopharyngeal testing kit was also positive.

On hospital day 8, the patient's respiratory status worsened and her oxygen saturation declined to 91% on ambient air. She was given two 400 mg doses of hydroxychloroquine followed by 200 mg twice daily. Within the next 48 hours, she had improvement in her abdominal pain and bloody diarrhea. Her respiratory symptoms did not evolve further, but she did require 5 L of oxygen via nasal cannula for several days. CT scan of the chest and CT angiogram of the abdomen and pelvis performed on hospital day 10 showed multifocal pneumonia consistent with pulmonary COVID-19 disease as well as resolution of colonic inflammation (Figure 3). There was no evidence of vascular compromise.

Over the next 12 days, the patient's respiratory status gradually improved and she was weaned off oxygen supplementation. Her digestive symptoms also improved. The patient was discharged on hospital day 20 in good health, off all antimicrobials. Unfortunately, at the time of the writing of this report, the patient has been readmitted with mental status changes that are currently being evaluated.

DISCUSSION

There has been a growing appreciation of the importance of digestive symptoms (nausea, vomiting, anorexia, non-bloody diarrhea, and abdominal pain) in the spectrum of COVID-19 disease. Presumed gastrointestinal manifestations have been reported in anywhere from 3-50% of patients with concomitant SARS-CoV-2 pulmonary infection (6, 7, 8, 12). SARS-CoV-2 RNA has been found in fecal samples from patients with COVID-19 pulmonary disease, and initial

case series have noted that 3-10% of patients who are eventually found to have SARS-CoV-2 pulmonary infection initially presented with isolated digestive symptoms (6, 8). What has been more difficult to establish is whether SARS-CoV-2 infection is directly responsible for the digestive symptoms. Since the focus of care in most hospitalized patients is the respiratory illness, and endoscopy—as a possible virus-aerosolizing procedure—is employed judiciously, diagnostic studies to implicate the virus in gastrointestinal pathology and to exclude other etiologies are generally not undertaken.

Because our patient presented with bloody diarrhea, which has not previously been described as a manifestation of COVID-19, and our index of suspicion in early March 2020 was low, our patient did undergo a comprehensive evaluation. This strongly suggested that SARS-CoV-2 gastrointestinal infection was responsible for her acute hemorrhagic colitis. We demonstrated that SARS-CoV-2 RNA was present in our patient's feces, and the endoscopic findings of coloproctopathy in her descending colon, sigmoid colon, and rectum confirmed colonic injury and pointed toward an infectious process. We were also able to eliminate, to the greatest extent possible, other potential etiologies of hemorrhagic colitis—such as alternative infections, inflammatory bowel disease, and ischemic colitis—through lab testing, radiological imaging, and colon and rectal biopsies. Although fecal molecular testing was performed after the initiation of antimicrobials, it is well described that even in the treated patient, fecal molecular testing will remain positive for up to several weeks (13). This, combined with the fact that our patient did not improve with standard antimicrobial therapy, makes a multi-infection scenario unlikely.

Interestingly, although our patient had endoscopic evidence of coloproctopathy and colonic thickening on CT, her sigmoid colon and rectal biopsies were histologically unremarkable. There is currently no commercially-available assay in the United States to test tissue for the presence of SARS-CoV-2 RNA, so we were not able to do this. However, such normal histologic findings are in line with the 2003 SARS-CoV experience wherein, under light microscopy, small intestinal and colonic specimens of patients with confirmed SARS-CoV gastrointestinal infection showed normal architecture, without evidence of villous atrophy, inflammatory infiltrates, or virocytes (14). We also did not have access to electron microscopy; in the 2003 SARS-CoV experience, viral particles were seen by electron microscopy in the small intestinal and colonic epithelial cells (15).

Related, there was also a disconnect between the degree of colonic inflammation seen on initial CT scan and the endoscopically-observed coloproctopathy seen on flexible sigmoidoscopy. We suspect this is because the CT scan was performed three days before the flexible sigmoidoscopy, and thus some healing was likely already taking place in at least the left colon. Moreover, on CT scan, the colonic inflammation was most pronounced in the ascending and transverse colon, with the left colon not too far behind. Our patient's continued bloody diarrhea post-flexible sigmoidoscopy was likely from resolving mucosal damage in the ascending and transverse colon that was not observed on flexible sigmoidoscopy.

It has become established that the target viral receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2) (9, 15, 16). This receptor is highly expressed on type II alveolar cells, esophagus epithelial cells, and both small intestine and colonic cells, among other cell types (9, 17, 18, 19). Additionally, immunofluorescence analysis has shown that the ACE2 receptor is abundantly expressed in also gastric and rectal epithelia (9). These data suggest that SARS-CoV-2 may gain entry into and potentially damage gastrointestinal host cells, causing the array of digestive symptoms that are currently being observed.

Our patient was taking lisinopril 40mg daily as part of her regimen for hypertension. There have been some reports suggesting that patients treated with ACE-inhibitors and angiotensin-receptor blockers may theoretically have increased numbers of ACE2 receptors, making them more prone to infection with SARS-CoV-2 and perhaps higher risk for severe COVID-19 disease (20). It is certainly plausible this applied to our patient. Our patient did clinically improve with hydroxychloroquine administration, and there have been some reports suggesting a possible benefit (21, 22). We are unsure whether this was truly a therapeutic effect or coincidental. More research is certainly needed in regards to the clinical efficacy of hydroxychloroquine in the treatment of SARS-CoV-2 infection.

From a transmission perspective, oral and respiratory droplets are well described as the major mode of transmission of SARS-CoV-2 viral particles. However, live SARS-CoV-2 virus has also been isolated from fecal samples and viral particles have been detected in the feces even after resolution of respiratory symptoms, suggesting the potential for fecal-oral transmission beyond the symptomatic period (9, 23). When our patient was admitted, she did not meet CDC guidelines at the time for PUI for SARS-CoV-2 infection as she was afebrile, had no respiratory symptoms, and had not travelled to China, Italy, Iran, or South Korea. We were unfortunately not aware of the *Washington Post* article that ran 3 days before her presentation, reporting a cluster of SARS-CoV-2 cases associated with Nile River cruises (24). Awareness of the gastrointestinal manifestations of SARS-CoV-2 may have increased our index of suspicion and encouraged us to institute SARS-CoV-2 precautions on arrival, avoiding the exposure and subsequent quarantine of 72 healthcare workers, including many of us.

To our knowledge, this is the first report of SARS-CoV-2 gastrointestinal infection causing hemorrhagic colitis in which colonic injury was demonstrated endoscopically and other etiologies were excluded. This case adds to the body of evidence implicating the gastrointestinal tract in the clinical expression and transmission of SARS-CoV-2 infection. On this basis, we believe it is important to institute SARS-CoV-2 precautions in patients who present with either respiratory *or* digestive symptoms. We also encourage the rapid development and deployment of fecal testing kits for SARS-CoV-2 RNA and encourage institutions to use their nasopharyngeal kits for fecal testing in the interim.

On March 29, 2020, New York City healthcare professionals made the recommendation that anyone presenting to New York City hospitals (even without respiratory or digestive

symptoms) be considered SARS-CoV-2 positive and appropriate safeguards taken (25). We have not reached this level universally in our country, yet. But this emerging disease will continue to evolve, and so must we. For the maxim "when you hear hoofbeats, think horses not zebras" works well, unless you are on a safari—or in the middle of a pandemic.

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Figure 1. Initial CT scan of the abdomen and pelvis in the emergency room. (A): Axial CT image of the lower thorax shows no airspace disease in the lungs. A small, right pleural effusion is present (arrow). (B, C, D): Intravenous contrast-enhanced CT scan of the abdomen and pelvis in the coronal (B & D) and axial (C) planes shows severe inflammation of the ascending colon (B), transverse colon (C), and descending colon (D), characterized by circumferential wall thickening, mural hyperenhancement, mesenteric hypervascularity, and pericolic fat stranding (arrows).
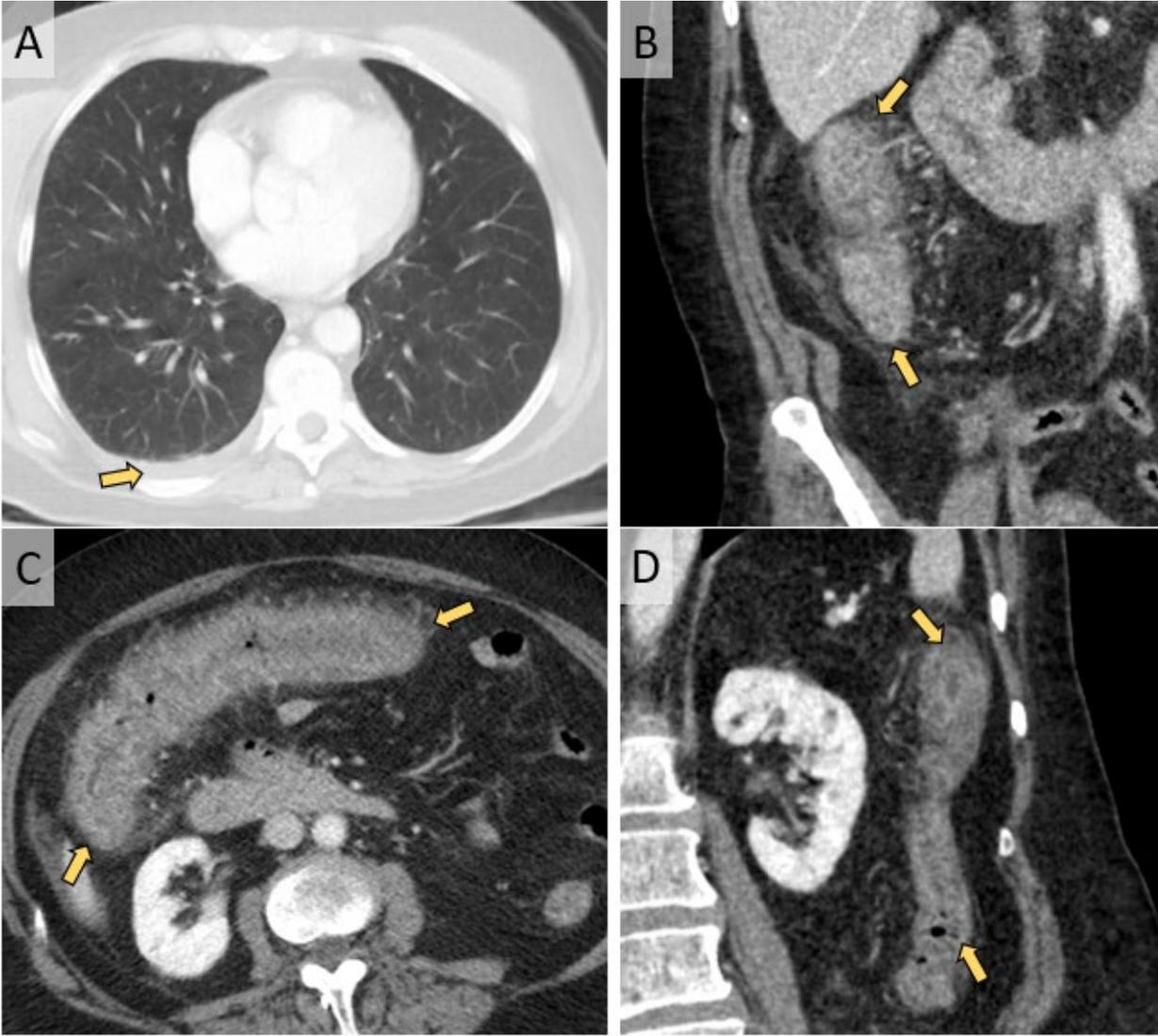
Figure 2. Descending colon and sigmoid colon on flexible sigmoidoscopic examination. The descending colon, sigmoid colon, and rectum contained patchy areas of focal erythema (arrows).
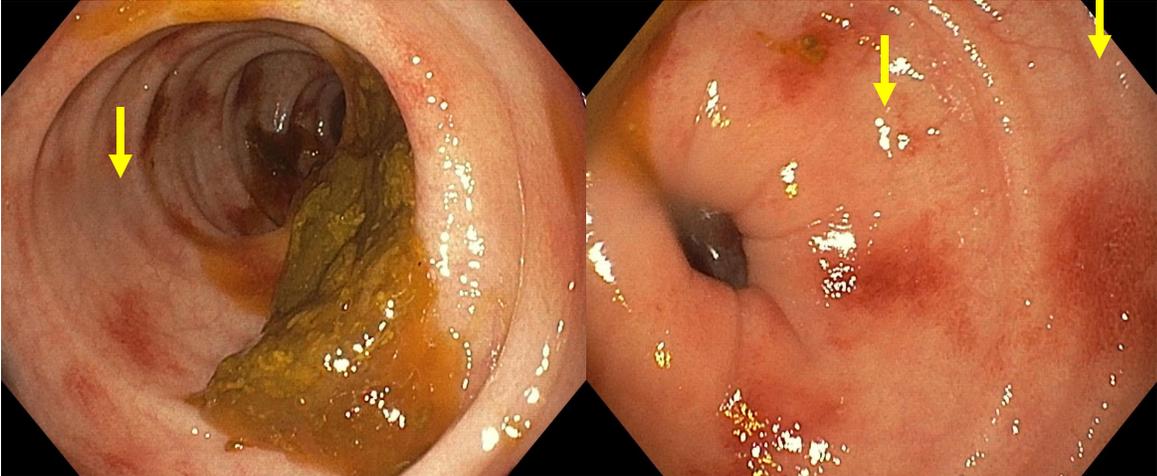

Figure 3: CT angiogram of the abdomen and pelvis on hospital day 9. Intravenous contrast-enhanced CT scan of the abdomen and pelvis in the coronal (A & C) and axial (B) planes shows resolution of the prior inflammation involving the ascending colon (A), transverse colon (B), and descending colon (C). Specifically, bowel wall thickening, mural hyperenhancement, mesenteric hypervascularity, and pericolic fat stranding (arrows) have resolved.