

The Many Faces of COVID-19: Atypical Presentation of COVID-19 in a Patient With Crohn's Disease With Acute Diarrhea Leading to Severe Hypovolemic Hyponatremia—A Case Report

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The outbreak of 2019 novel coronavirus, now renamed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the World Health Organization, was first described in December 2019 in Wuhan, China (1). With the exponential increase in coronavirus disease 2019 (COVID-19) cases in countries, such as the United States, with a higher prevalence of patients with inflammatory bowel disease (IBD), the implications of COVID-19 for patients with IBD are unclear, given that there are no large data set studies on patients with IBD.

Here, we describe a patient with ileocolonic Crohn's disease on azathioprine (AZA) who was diagnosed with COVID-19 and found to have acute diarrhea leading to severe hypovolemic hyponatremia.

A 60-year-old White gentleman, with a history of hypertension on losartan and ileocolonic Crohn's disease status after remote subtotal colectomy with ileosigmoid anastomosis in sustained clinical remission and stable postsurgery endoscopic remission (11 Rutgeerts grade on ileocolonoscopy 2 months ago) on AZA 175 mg (2 mg/kg) daily, presented to the emergency department with 3 days of mild cough, watery diarrhea, diffuse myalgias, and subjective fever. On presentation to the emergency department, the patient was with stable vital signs and a pulse oximeter reading of 98% on room air. Laboratory evaluation was remarkable for lymphopenia at 0.48/mm³ (K/uL), and hyponatremia with Na at 123 mmol/L. Serum creatinine and blood urea nitrogen levels were normal at 0.82 and 9 mg/dL, respectively. Other pertinent laboratory test results included low serum osmolality at 264 mmol/kg, normal thyroid stimulating hormone at 3.56 mIU/L, and normal serum cortisol at 15.5 µg/dL. Influenza and respiratory syncytial virus polymerase chain reactions (PCRs) were negative; however, COVID-19 nasopharyngeal swab PCR was positive. Chest x-ray was unremarkable. Infectious disease was consulted, and he was started on hydroxychloroquine 200 mg twice a day for 4 days. Nephrology was consulted, and the patient was discharged with salt tablets for quarantine at home and was advised to stop AZA. However, 4 days after discharge, the patient represented with worsening generalized weakness, nausea, and continuous watery diarrhea. Laboratory test results were remarkable for worsening hyponatremia (Na 121 mmol/L), new leukopenia (2.9 K/uL), and worsening lymphopenia (0.40 K/uL). Stool studies including *Clostridium difficile* PCR were negative. The patient was admitted and administered continuous normal saline infusion with incrementation of Na to 130 mmol/L. Along with Na incrementation, the patient's diarrhea resolved with continued supportive management. At this point, the presence of the patient's severe hyponatremia was attributed to severe acute

diarrhea, a known GI manifestation of COVID-19.

To our knowledge, this is the first case report of a patient with ileocolonic Crohn's disease and COVID-19 presenting with severe hyponatremia. Although multiple studies in the past have described opportunistic viral infections such as varicella zoster virus, herpes simplex virus, cytomegalovirus, and Epstein-Barr virus in the IBD population (2), data on SARS-CoV-2 in IBD are sparse. Furthermore, the SARS-CoV-2 infection is not an opportunistic viral infection, given that it is extremely contagious.

There is a hypothetical, yet unproven reason to believe that patients with IBD may be at higher risk of SARS-CoV-2-induced infection. Coronaviruses are known to bind to their target cells through angiotensin-converting enzyme 2 [ACE2]. ACE2 is expressed by epithelial cells of the lung, kidney, blood vessels, intestine; and the terminal ileum and colon have higher concentrations of ACE2. Furthermore, proteomic analysis of tissue samples of patients with IBD has demonstrated a higher expression of ACE2 in Crohn's disease compared with ulcerative colitis (3). This mechanism might explain diarrhea as one of the presenting complaints of our patient with known ileocolonic Crohn's disease. In a recent meta-analysis of 4,243 COVID-19 patients from 6 countries, the pooled prevalence of diarrhea was 12.5% (4).

Hyponatremia is a known manifestation of hospitalized patients with acute diarrhea with up to 67.8% presenting with hyponatremia on admission (plasma Na <137 mEq/L) (5). However, hyponatremia due to acute infectious diarrhea in patients with Crohn's disease may be more pronounced because it is known that up to 33% of patients with Crohn's disease may have low levels of serum sodium at baseline, alone or in combination with other electrolytes (6). Furthermore, our patient had a subtotal colectomy, and previous studies (7) have shown that sodium absorption in proctocolectomized patients with radiologically normal small bowel and in clinical remission have markedly reduced sodium absorption. This might be explained by the fact that the electrogenic absorption of water and Na is located at the surface epithelium and upper crypts of the distal colon,

and the electroneutral absorption of water and Na is located in crypts and surface epithelium of the proximal and distal colon (8). Thus, hyponatremia due to diarrhea in COVID-19 may be more severe in patients with Crohn's disease with previous colonic surgery, as was the case in our patient.

Hyponatremia is a common clinical complication in the setting of infection via several underlying pathophysiological mechanisms that might overlap (9). The etiological classification of hyponatremia is based on serum osmolality and volume status. Hyponatremia due to Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) is a common complication of pulmonary infection due to lung congestion and decreased pulmonary venous return that leads to activation of the volume receptors and causes increased antidiuretic hormone secretion (10). One of the major criteria for SIADH diagnosis is clinical euvolemia as defined by the absence of hypervolemia or hypovolemia. Our patient was hypovolemic on initial presentation, which excludes SIADH. Adrenal insufficiency has been reported as a cause of hyponatremia in infection; however, our patient had a normal cortisol level on presentation. In our reported case, the patient had low serum osmolality and hyponatremia that improved with volume repletion alone, which supports our claim that hyponatremia is mainly secondary to diarrhea and resultant hypovolemia.

In addition, ACE2 expression in urinary organs (kidney) is known to be nearly 100-fold higher than in respiratory organs and may increase risk of acute kidney injury in patients with COVID-19 (11), which may further contribute to hyponatremia. Although our patient's blood urea nitrogen and Cr levels were not elevated, studies have shown that individuals with COVID-19 might have early renal injury with normal serum creatinine that may cause hyponatremia (12). Our patient was also on losartan, and ACE2 is a functional receptor for SARS-CoV-2. However, the safety and potential effects angiotensin-receptor blockers in patients with COVID-19 has not been established, and further evidence is needed to support the continuation or cessation of angiotensin-receptor blockers in patients with COVID-19 (13).

Data from China so far have shown that chronic obstructive pulmonary disease, diabetes, hypertension, and malignancy are risk factors for severe COVID-19 disease leading to admission to intensive care unit

(ICU), invasive ventilation, or death (14). Furthermore, among laboratory characteristics, data from Wuhan (15) have identified lower lymphocyte count to be associated with severe COVID-19 pneumonia with a worse prognosis leading to ICU admission, mechanical ventilation, or death. Our patient did have hypertension and lymphocytopenia as predictors of worse prognosis and was also on AZA before admission, an immunosuppressant known to increase risk of infections by decreasing the number of activated T-cells and inhibiting intracellular signals needed by the host to fight pathogens (16).

Our patient did well with supportive treatment, did not require ICU admission, and was discharged on improvement of hyponatremia and diarrhea. Congruent with recommendations made by the International Organization of IBD (17), AZA was stopped on development of COVID-19 symptoms and positive PCR test for SARS-CoV-2 with plans to restart AZA on complete resolution of symptoms (cough).

Further data on the epidemiology and prognosis of COVID-19 in patients with IBD are needed to inform management decisions. This case has been reported to the SECURE-IBD registry accessible at <https://covidibd.org>, which is an international collaborative effort to define the impact of COVID-19 on patients with IBD.

CONFLICTS OF INTEREST

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