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CASE REPORT | INFLAMMATORY BOWEL DISEASE

De Novo Crohn's Disease Triggered After COVID-19: Is COVID-19 More Than an Infectious Disease?

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ABSTRACT

Coronavirus disease 2019 (COVID-19)-associated immune dysregulation is believed to trigger the onset of various autoimmune diseases. These occur either during active COVID-19 or soon after recovery. We report ileocolonic Crohn's disease in a 35-year-old woman after her recovery from a milder form of COVID-19. She achieved remission of her symptoms with oral corticosteroids and sulfasalazine.

INTRODUCTION

Inflammatory bowel disease (IBD) pathophysiology involves a complex interplay between genetic, environmental, and microbial factors and immune responses. Both adaptive immunity and innate immunity play a significant role in its pathogenesis.[1] There are established links between enteric infection-related dysbiosis and the future development of IBD.[2] The current coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has impacted almost all the diseases, and IBD is not an exception. There are several reports of triggering of autoimmune conditions during active COVID-19 or after recovery from it.[3,4] Rheumatologists have started to understand the increased risk of rheumatic disease in patients with COVID-19.[5] However, the concept of "triggering of IBD after COVID-19" is still naive. The occurrence of de novo ulcerative colitis after COVID-19 infection has already been reported.[6] We report a case of de novo Crohn's disease in a young woman triggered soon after recovery from COVID-19.

CASE REPORT

A 33-year-old woman with no medical history had presented with a sore throat, fever, and myalgia in July 2020. She did not have cough, breathlessness, or gastrointestinal symptoms. A nasopharyngeal reverse transcription-polymerase chain reaction swab was positive for SARS-CoV-2. Thoracic radiograph was unremarkable, and laboratory tests showed hemoglobin 11.1 g/dL, platelet count 405×10^9/L, serum albumin 4.1 g/dL, and C-reactive protein 12 mg/dL. She received acetaminophen and was advised of home isolation. Her symptoms improved in a week. But, over the next 2 weeks, she developed large volume, watery, and nonbloody diarrhea associated with periumbilical pain. She developed oral ulcers, joint pains, and lost 13 kg of weight over the next 6 weeks. She denied any previous episodes of similar symptoms, and her physical examination showed pallor and swelling of multiple small joints of both the upper and lower limbs. Digital rectal examination revealed fissure-in-ano.

Repeat laboratory tests showed hemoglobin 8.5 g/dL, platelet count 620×10^9/L, serum albumin 2.9 g/dL, erythrocyte sedimentation rate 120 mm/hr, C-reactive protein 90 mg/dL, and fecal calprotectin level more than 800 μg/g. Stool microscopy, culture, and sensitivity did not reveal any pathogens. The patient was negative for HLA-B27 and antinuclear antibody. Her repeat nasopharyngeal reverse transcription-polymerase chain reaction swab was negative for SARS-CoV-2. Ileocolonoscopy showed multiple focal ulcers with normal intervening mucosa from the descending colon up to the terminal ileum with rectal sparing (Figure 1). Histopathology

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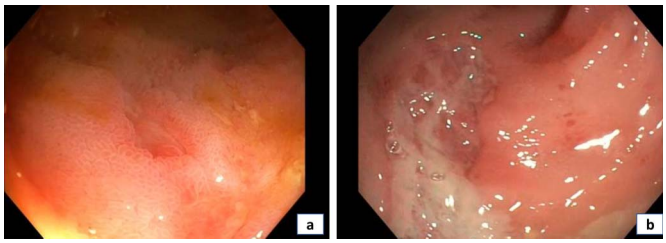

Figure 1. Ileocolonoscopy showing (A) ulcer in the terminal ileum and (B) focal colonic ulcers with normal intervening mucosa.

of the ulcers revealed focal architectural distortion, cryptitis, dense lymphoplasmacytic infiltration in the lamina propria, and ill-defined epithelioid cell granulomas in the submucosa (Figure 2). Computed tomography enterography showed increased mesenteric vascularity, segmental wall thickening, and mucosal hyperenhancement in the terminal ileum, ileocecal junction, cecum, and multiple focal areas in the colon (Figure 3). Based on the above investigations, we diagnosed de novo Crohn's disease. She was started on oral prednisone 0.75 mg/kg, and the rheumatologist suggested sulfasalazine 2 g daily for her arthritis. Her joint pain and diarrheal episodes decreased gradually over the next 3 weeks. She is currently in clinical remission, and her follow-up laboratory tests after 1 month showed hemoglobin 10.1 g/d, platelet count 410 $\times$ 10^9/L, and erythrocyte sedimentation rate 32 mm/hr. We advised tapering steroids over the next 8 weeks. The need and the timing of maintenance therapy will be assessed based on the disease behavior during the follow-up.

DISCUSSION

The ongoing COVID-19 pandemic has unveiled many clinical challenges because of its unpredictable disease kinetics. The clinical spectrum of COVID-19 ranges from asymptomatic or minor respiratory illness to respiratory failure and even multiorgan dysfunction syndrome. Even after recovery, patients may have long-term sequelae. There are reports of the development of autoinflammatory conditions and autoimmune diseases after recovery from COVID-19.[3–5,7] Dysregulated immune response is proposed to play a vital role in pathogenesis.

Infections are one of the triggers for autoimmune diseases.[8] Viruses cause loss of self-tolerance by molecular mimicry, bystander activation, and epitope spreading.[9] It is believed that COVID-19 also produces similar inflammatory immune responses. Complement consumption,[10] immune complex deposition,[11] development of antinuclear antibodies, and anti-DNA antibodies[12] are speculated in the COVID-19 autoimmunity phenomenon. SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE-2) receptors and leads to immune activation and redistribution of immune cells. It causes cytokine-mediated bone marrow suppression and increased apoptosis of lymphocytes. The immune cells may be clustered at the sites of inflammation such as lungs and intestine, leading to a reduction in peripheral lymphocytes. This relative peripheral lymphopenia

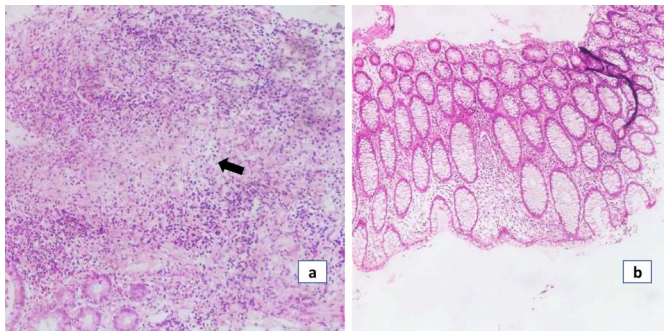

Figure 2. Photomicrographs of ileocolonic mucosal biopsy: (A) arrow points to an ill-defined granuloma (hematoxylin and eosin stain, 40$\times$ magnification) and (B) crypt architectural distortion (hematoxylin and eosin stain, 20$\times$ magnification).

causes loss of tolerance to self. Once the patient recovers from COVID-19, the cytokine surge settles, and the lymphocyte count increases. In the setting of loss of self-tolerance, this produces an immune reconstitution and unregulated immune response.[13] This, along with the environmental and genetic factors, can unveil an autoimmune disease. Rodríguez et al[14] conceptualized that COVID-19 may be more than an infectious disease. Autoimmunity and autoinflammatory conditions are at its crossroad.

IBD is a chronic relapsing-remitting or continuously active idiopathic inflammatory bowel disorder characterized by an inappropriate, dysregulated immune response to luminal antigens leading to overproduction of proinflammatory cytokines.[15] The ACE-2 receptors are present in the lungs, terminal ileum, and colon. The tissue concentration of the ACE-2 receptor and the serine protease (an enzyme that activates the spike protein of SARS-CoV-2) increases in IBD.[16,17] Hence, SARS-CoV-2 theoretically can cause direct virus-related and immune dysregulation–related intestinal inflammation. It can create a milieu for intense intestinal inflammation in susceptible individuals. When such inflammation occurs along with defective downregulation in susceptible individuals, it can trigger IBD onset.

Dysbiosis is one of the pathomechanisms of IBD.[2] The gastroenteritis occurring because of COVID-19 leads to dysbiosis.[18] Dysbiosis results in increased gut permeability. Such disruption

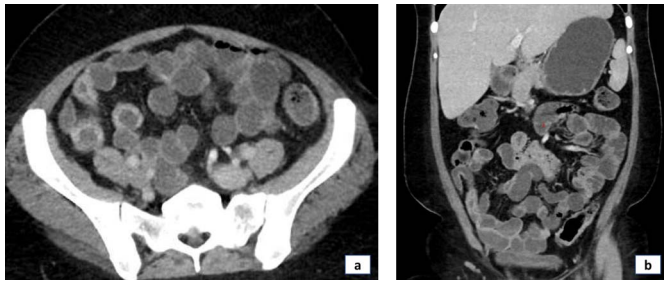

Figure 3. Computed tomography enterography showing (A) mucosal hyperenhancement and wall thickening in the ileocecal and ascending colon and (B) segmental wall thickening of the bowel.

of the gut barrier integrity may lead to translocation of SARS-CoV-2 from the lung into the intestinal lumen through circulatory and lymphatic system.[19] Increased gut permeability may also provoke more stimulation of mucosal immune cells by the luminal antigens. It can perpetuate intestinal inflammation.[20] In this case, we also considered tuberculosis, vasculitis, ischemic colitis, nonsteroidal anti-inflammatory drug–induced ulcers, and direct cytotoxicity of the SARS-CoV-2 as possibilities. However, the absence of nonsteroidal anti-inflammatory drug intake, morphology and distribution of the ulcers, and characteristic histology favored Crohn's disease. The temporal relationship to COVID-19, absence of bowel symptoms in the past, and normal laboratory investigations during the initial diagnosis of COVID-19 support its de novo occurrence.

In conclusion, COVID-19 can cause immune dysregulation and trigger autoimmune disorders in susceptible individuals. Hence, it is prudent to follow these patients after recovery from COVID-19. It may even be appropriate to think of COVID-19 beyond an infectious disease owing to its effects on the immune system.

DISCLOSURES

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