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Case report

Ulcerative colitis as a possible sequela of COVID-19 Infection: The endless story

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A B S T R A C T

The coronavirus disease 2019 (COVID-19), caused by the novel coronavirus SARS-CoV-2, is a new type of acute infectious respiratory syndrome that usually presents with mild flu-like symptoms. However, the disease caused widespread illness and death worldwide, and new sequelae are still being discovered. SARS-CoV-2 RNA was isolated from the fecal samples of some infected patients. Many pathogens, including many viral infections, were linked either to the onset or the exacerbation of inflammatory bowel disease (IBD). With this, we report a series of 2 IBD cases that were diagnosed shortly after recovery from COVID-19. This is the first report that discusses the possibility of developing IBD following COVID-19 infection to the best of our knowledge. This could highlight the importance of thoroughly investigating COVID-19 patients who presented with diarrhea, particularly those with bloody diarrhea, and not consider it a simple manifestation of COVID-19 infection.

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Introduction
The coronavirus disease 2019 (COVID-19), caused by the novel SARS-CoV-2, is a new acute infectious respiratory syndrome identified in December 2019 [1]. The most commonly encountered clinical presentation of the disease is mild flu-like symptoms; however, the disease may cause severe and frequently lethal complications such as progressive pneumonia, Acute Respiratory Distress Syndrome (ARDS), and eventually organ failure due to hyperinflammation and cytokine storm syndrome [2]. There is great evidence that COVID-19 results in activation of the infected host’s innate and adaptive immune cell response [3]. Also, Angiotensin Converting Enzymes (ACE2) as COVID-19 receptors are highly expressed in the intestinal epithelial cells from the terminal ileum down to the colon to a lesser extent; the site where mucosal inflammation in Inflammatory bowel diseases (IBD) patients is frequently detected [4]. One of the possible mechanisms in IBD pathogenesis is that the adaptive immune system cells respond against self-antigens producing chronic inflammatory conditions [5]. COVID-19 can increase the risk of developing new autoimmune diseases, including antiphospholipid syndrome, Guillain-Barré syndrome, Kawasaki disease, and others [6]. With this, we report for the first time a series of 2 IBD cases that were diagnosed shortly after recovery from COVID-19. Table 1.

Case series

Case 1. A 37 years old male patient was diagnosed with COVID-19 infection with mainly respiratory symptoms of moderate severity that needed a short course of steroid therapy to control. He is a pharmacist with an urban residence. Two months after COVID-19 recovery, the patient suffered from bloody diarrhea, having eight painless bowel movements per day with no fever or weight loss. Colonoscopy examination revealed proctosigmoiditis with moderate severity (Fig. 1). The histopathological assessment confirmed the diagnosis of ulcerative colitis with no dysplasia (Fig. 2), and the patient received an induction course of steroids and mesalazine with a good clinical response.

Case 2. A 64 years old male patient, a veterinary worker with urban residency, had COVID-19 infection with mild constitutional symptoms for seven days followed by respiratory symptoms of mild severity for...
another seven days. There was no indication to administer steroids or immunosuppressives. Three weeks following recovery, the patient suffered abdominal pain and diarrhea for 2wks that became bloody with no response to intestinal antiseptics and antidiarrheal agents. The patient denied using any laxatives, and none of the patients’ contacts had a similar complaint. The patient is not known to be diabetic nor hypertensive, and he had a colonoscopy that revealed the presence of proctosigmoiditis with moderate severity (Fig. 3). The histopathology confirmed the diagnosis of ulcerative colitis with no dysplasia.

Table 1

| Variables                                      | Case 1     | Case 2     |
|------------------------------------------------|------------|------------|
| Sociodemographic                               |            |            |
| Age (years)                                    | 37         | 64         |
| Gender                                         | Male       | Male       |
| Smoking                                        | No         | Yes        |
| Residence                                      | Urban area | Urban area |
| Occupation                                     | Pharmacist | Veterinary worker |
| DM                                             | No         | Yes        |
| HTN                                            | No         | Yes        |
| Liver disease                                  | No         | No         |
| Autoimmune diseases                            | No         | No         |
| COVID-19 related symptoms                      |            |            |
| Clinical presentation                          | Respiratory symptoms | Respiratory symptoms |
| Disease severity                               | Moderate   | Mild       |
| Steroid therapy                                | Yes        | No         |
| Immunosuppressives                             | No         | No         |
| Fever                                          | No         | No         |
| Abdominal pain                                 | No         | Yes        |
| Bloody Diarrhea                                | Yes        | Yes        |
| IBD extraintestinal manifestations             | No         | No         |
| Comorbidities                                  |            |            |
| DM                                             | No         | Yes        |
| HTN                                            | No         | Yes        |
| Liver disease                                  | No         | No         |
| Autoimmune diseases                            | No         | No         |
| DM                                              | No         | Yes        |
| HTN                                            | No         | Yes        |
| Liver disease                                  | No         | No         |
| Autoimmune diseases                            | No         | No         |
| COVID-19 related symptoms                      |            |            |
| Clinical presentation                          | Respiratory symptoms | Respiratory symptoms |
| Disease severity                               | Moderate   | Mild       |
| Steroid therapy                                | Yes        | No         |
| Immunosuppressives                             | No         | No         |
| Fever                                          | No         | No         |
| Abdominal pain                                 | No         | Yes        |
| Bloody Diarrhea                                | Yes        | Yes        |
| IBD extraintestinal manifestations             | No         | No         |
| IBD related symptoms                           |            |            |
| Fever                                          | No         | No         |
| Abdominal pain                                 | No         | Yes        |
| Bloody Diarrhea                                | Yes        | Yes        |
| IBD extraintestinal manifestations             | No         | No         |
| Time before appearance of IBD symptoms (weeks) | 8          | 3          |
| Lab. finding                                   |            |            |
| WBCs ($10^{9}$/L)                               | 4.6        | 8.6        |
| HB (g/dL)                                      | 10.9       | 12         |
| PLT ($10^{9}$/L)                                | 186        | 377        |
| S. Albumin (g/dL)                              | 4.1        | 3.7        |
| ALT (U/L)                                      | 32         | 26         |
| AST (U/L)                                      | 29         | 24         |
| ALP (U/L)                                      | 218        | 121        |
| INR                                            | 1.1        | 1.1        |
| S. Creatinine (mg/dL)                          | 0.9        | 1.1        |
| CRP (mg/L)                                     | 65         | 98         |
| ESR (mm/hr)                                    | 29         | 35         |
| Fecal calprotectin (µg/g)                      | 185        | 350        |
| Serum Ferritin (ng/mL)                         | 325        | 311        |
| Colonoscopy                                    |            |            |
| Disease extent                                  | Proctosigmoiditis | Proctosigmoiditis |
| Disease severity                               | Moderate   | Moderate   |
| Histopathology                                  |            |            |
| Diagnosis                                      | UC         | UC         |
| Dysplasia                                      | No         | No         |

ALT: Alanine Aminotransferase, AST: Aspartate aminotransferase, CRP: C-Reactive Protein, DM: diabetes mellitus, ESR: Erythrocyte sedimentation rate, HB: hemoglobin, HTN: Hypertension, IBD: inflammatory bowel disease, INR: international normalized ratio, PLT: platelets, ALP: Alkaline Phosphatase, UC: ulcerative colitis, WBC: white blood count
The patient started induction therapy with steroids and mesalamine. Complete clinical and laboratory data of the presented cases are detailed in table 1.

Discussion

Many reports provided evidence about the ability of infections to precipitate autoimmune diseases [6,7]. Many bacterial, viral, parasitic, and even fungal pathogens have been linked to the onset or the exacerbation of IBD [8,9]. In these cases, the causative organism is not necessarily isolated from the gastrointestinal cells, and the enhanced inflammatory response after infection can eliminate the infectious agent. However, in genetically susceptible people to IBD, this initial immune reaction can turn into a chronic response, leading to IBD [10].

Despite that SARS-CoV-2 affects mainly the respiratory system, many reports stated the presence of gastrointestinal manifestations, like nausea, vomiting, abdominal pain, and diarrhea [15–18]. Furthermore, SARS-CoV-2 RNA was isolated from the fecal samples of some infected patients [18,19]. Angiotensin-Converting Enzyme II (ACE2), the primary binding site for SARS-CoV-2, is markedly expressed in the GIT and many other organs. SARS-CoV-2 induces enteritis and diarrhea by activating the intestinal ACE2 receptors [20,21]. Intestinal infection by SARS-CoV-2 causes microbiome dysbiosis by altering the intestinal immune system. The activation of the enteric immune system sends inflammatory signals to the circulation and other organs. If the condition worsens and acute respiratory distress syndrome (ARDS) develops, the intestinal symptoms decrease. This reduction may reincrease if the cytokines storm develop [21]. Some case reports showed that COVID-19 infection might present with colitis which can be hemorrhagic [22,23]. One case report was published for a COVID−19 infection kidney transplant presented with bloody diarrhea. The colonoscopy in this patient showed ulcers in the terminal ileum; however, the biopsy showed chronic active ileitis without clear evidence of Crohn’s disease [24]. Either classic GI infections or dysbiosis can initiate IBD in genetically susceptible patients. This is the first time to report IBD development following COVID-19 infection to the best of our knowledge.

Severe COVID-19 is characterized by a cytokine storm in which there are extensive neutrophils, lymphocytes, macrophages, and immune mediators, including Tumor Necrosis Factor (TNF). TNF was detected in blood and tissue samples of some COVID-19 patients [25]. Anti-TNF biological therapies were suggested to treat SARS-CoV-2 infection [26]. It is well known that TNF is a principal inflammatory mediator in IBD and nearly all acute inflammatory reactions [26]. TNF is a key player in the innate immune responses in IBD patients, as it regulates the activation, proliferation, survival, and differentiation of intestinal innate immune cells [27]. So, TNF may be the main culprit in IBD development in cases with COVID-19.

This is the first report that raises the possibility of developing IBD following COVID-19 infection to the best of our knowledge. This article tries to warn about the possibility of developing IBD either concurrent with or following COVID-19 infection. It is not possible to confirm that we will face an increased incidence of IBD cases in the near future secondary to SARS-CoV-2 infection. However, it is vital to thoroughly investigate COVID-19 patients who presented with diarrhea, particularly those with bloody diarrhea, and not consider it a simple manifestation of COVID-19 infection.

Ethical considerations

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the participants included in the study.

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