

Case Report

Severe Refractory Diarrhea Associated with COVID-19: A Case Report

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Keywords

COVID-19 · Enterocolitis · Prednisolone · Case report

Abstract

Introduction: Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is frequently associated with various gastrointestinal symptoms, including abdominal pain, vomiting, and diarrhea. Moreover, several cases of refractory diarrhea have been reported after COVID-19 recovery. Herein, we present a case of severe refractory diarrhea associated with COVID-19. **Case Presentation:** A 50-year-old man with no comorbidities was admitted to our hospital with SARS-CoV-2 pneumonia. His respiratory status deteriorated, and ventilatory management, including extracorporeal membrane oxygenation, was needed. The patient's respiratory condition improved, resulting in a transfer to another hospital for rehabilitation. However, the patient developed diarrhea that worsened to 6,000–7,000 mL/day, and he was transferred to our hospital. We diagnosed the patient with enterocolitis caused by cytomegalovirus infection and treated him with ganciclovir on day 5 after transfer to our hospital. The diarrhea did not improve. We suspected enterocolitis associated with COVID-19 and administered a methylprednisolone pulse (intravenous injection, 1,000 mg/day for 3 days) on day 10 after transfer, resulting in a marked improvement in his symptoms. The prednisolone dose was tapered, and no recurrence of diarrhea was observed thereafter. **Conclusion:** The prevalence of COVID-19-associated enterocolitis is low, and the pathogenesis of the disease remains unclear. Prednisolone administration should be considered in cases of post-COVID-19 symptoms of severe diarrhea due to a possible abnormal immune response related to COVID-19.

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Introduction

Coronavirus disease 2019 (COVID-19), an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), mainly presents with respiratory symptoms with severe cases requiring ventilatory management, including extracorporeal membrane oxygenation [1]. However, several non-respiratory symptoms have also been reported to be associated with COVID-19.

SARS-CoV-2 is transmitted via the angiotensin-converting enzyme-2 (ACE-2) receptor following cleavage of its surface spike protein by a serine protease [2]. Patients with SARS-CoV-2 infection mainly present with respiratory symptoms because the ACE-2 receptor is highly expressed in the tracheal and type 2 alveolar epithelia [3]. However, ACE-2 receptors are also strongly expressed in the gastrointestinal mucosa, particularly in the small and large intestines [4]. Therefore, patients with COVID-19 often present with gastrointestinal (GI) symptoms including diarrhea and vomiting [5]. GI symptoms, including vomiting and diarrhea, are reported in approximately 10% of patients with COVID-19 [6], especially in the early phase. Recently, post-COVID-19 symptoms have been reported [7]. A systematic review reported that 22% of patients with post-COVID-19 had GI symptoms, while 10% had diarrhea [7]. Recently, several cases of severe diarrhea after COVID-19 have been reported [8–15]. The etiology and effective treatment of severe diarrhea associated with COVID-19 remain unknown. Therefore, this report presents a case of COVID-19-associated enterocolitis treated with prednisolone (PSL).

Case Report

A 50-year-old man without any medical conditions was admitted to our hospital with pneumonia caused by COVID-19. Although he was treated with glucocorticoids, his respiratory status deteriorated. Mechanical ventilation was initiated on day 7 after onset of COVID-19 symptoms, and extracorporeal membrane oxygenation support was provided on day 9. Subsequently, his respiratory condition improved, and tracheostomy was performed on day 20 after onset. He was transferred to another hospital for rehabilitation with a tracheostomy. He experienced diarrhea before the transfer on day 43 after the onset of COVID-19, which gradually worsened to 6,000–7,000 mL/day after the transfer; accordingly, he was transferred back to our hospital.

The patient was transferred to our hospital on day 62 after the onset of COVID-19 symptoms. When admitted to our hospital, he had watery diarrhea but no bloody stools. On physical examination, he had a temperature of 36.5°C, a pulse rate of 117 beats per minute, and a blood pressure of 120/83 mm Hg. His weight before the onset of COVID-19 was 114.5 kg (body mass index, 36.5 kg/m²), which decreased to 94.6 kg at the time of readmission to our hospital. Contrast-enhanced computed tomography revealed severe edema of the colon and intestinal fluid accumulation of the entire small bowel (shown in Fig. 1a). Blood tests revealed anemia (hemoglobin, 6.3 g/dL), severe hypoalbuminemia (albumin, 1.0 g/dL), mildly elevated d-dimer levels (3.1 µg/mL), and markedly elevated IL-6 levels (62.6 pg/mL). Stool tests were negative for *Clostridioides difficile* toxin A/B and glutamate dehydrogenase. Moreover, stool cultures were negative for causative bacteria of enterocolitis, including pathogenic *Escherichia coli* and *Clostridioides difficile*. Esophagogastroduodenoscopy revealed villous enlargement and ring-like erosions in the duodenum (shown in Fig. 1b). Capsule endoscopy revealed ring-shaped and multiple map-like ulcerations with villous enlargement in the entire small bowel and duodenum (shown in Fig. 1c). Colonoscopy revealed extensive mucosal edema and multiple shallow map-like ulcerations throughout the colorectal mucosa (shown in Fig. 1d, e). Examination of a biopsy specimen of colonic and small bowel mucosa revealed regenerative changes in the superficial epithelium and inflammatory cell infiltration in the mucosal layer. A PCR test

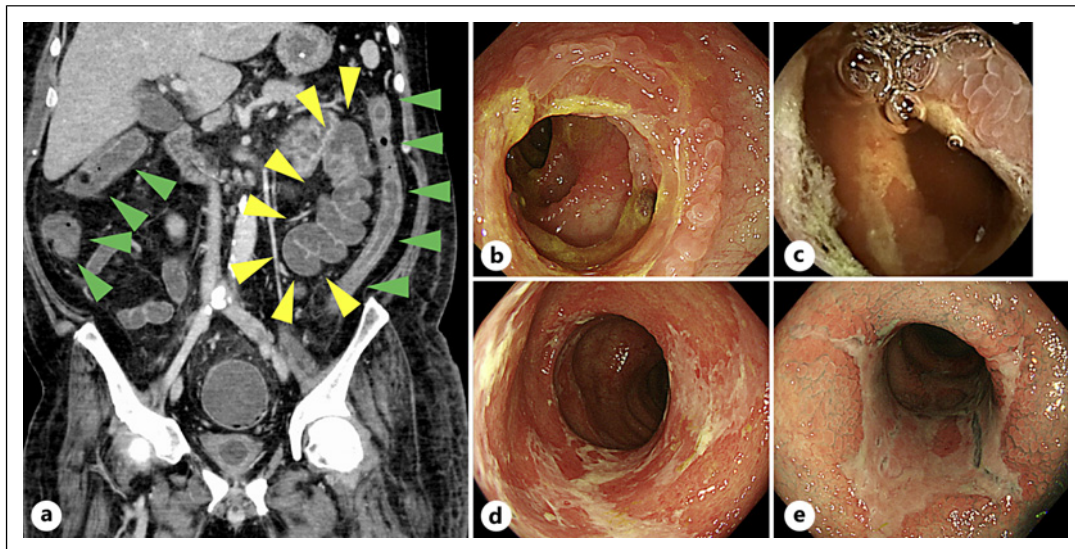


Fig. 1. Computed tomography and endoscopic images. **a** Computed tomography. **b** Duodenal mucosa by esophagogastroduodenoscopy. **c** Small bowel mucosa by capsule endoscopy. **d** Transverse colon. **e** Sigmoid colon by colonoscopy. Contrast-enhanced computed tomography revealed severe edema of the colon (green arrows) and intestinal fluid accumulation of the entire small bowel (yellow arrows) (**a**). Esophagogastroduodenoscopy revealed villous swelling and ring erosions in the duodenal mucosa (**b**), while no abnormalities were observed in the esophagus or stomach. Capsule endoscopy revealed villous swelling, erosions, and shallow ulceration throughout the small bowel mucosa (**c**). Colonoscopy revealed a shallow ulceration in the entire colonic mucosa (**d, e**).

for SARS-CoV-2 in the colonic mucosa was negative. No findings suggested vasculitis, thrombus formation, or inflammatory bowel disease in the biopsy specimens. The biopsy specimens revealed nuclear inclusion bodies. Moreover, immunohistochemistry was positive for the cytomegalovirus (CMV) antigen. In addition to the histological examination, a blood test revealed the presence of the CMV pp65 antigen C7HRP (7 pp65 antigen positive/100,000 white blood cells). The patient was diagnosed with enterocolitis caused by a CMV infection and treated with ganciclovir on day 5 after transfer to our hospital; however, the diarrhea did not improve. A progress chart is shown in Figure 2. We suspected enterocolitis associated with COVID-19 and attempted treatment with a methylprednisolone pulse (intravenous injection, 1,000 mg/day for 3 days) on day 10 after transfer based on a report of a severe diarrhea case in post-COVID-19, similar to GVHD, reported by Ozawa et al. [8]. The severity of diarrhea markedly improved after methylprednisolone administration. Secular changes in endoscopic images of the sigmoid colon are presented in Figure 3a–d. Blood tests were negative for C7HRP on day 14, and IL-6 decreased to 22.6 pg/mL on day 43. After tapering the PSL dose to 15 mg/day, the patient was transferred back to the referral center on day 49 after the transfer. The patient was weaned from PSL and discharged without any diarrhea flare-ups. One year has passed since the termination of steroid administration, and he has had no recurrence of diarrhea.

Discussion

Herein, we report a case of severe diarrhea associated with COVID-19. GI symptoms, such as diarrhea and vomiting, have also been reported in approximately 10% of COVID-19 cases [6]. Several cases of enterocolitis with severe diarrhea after COVID-19 treatment have been

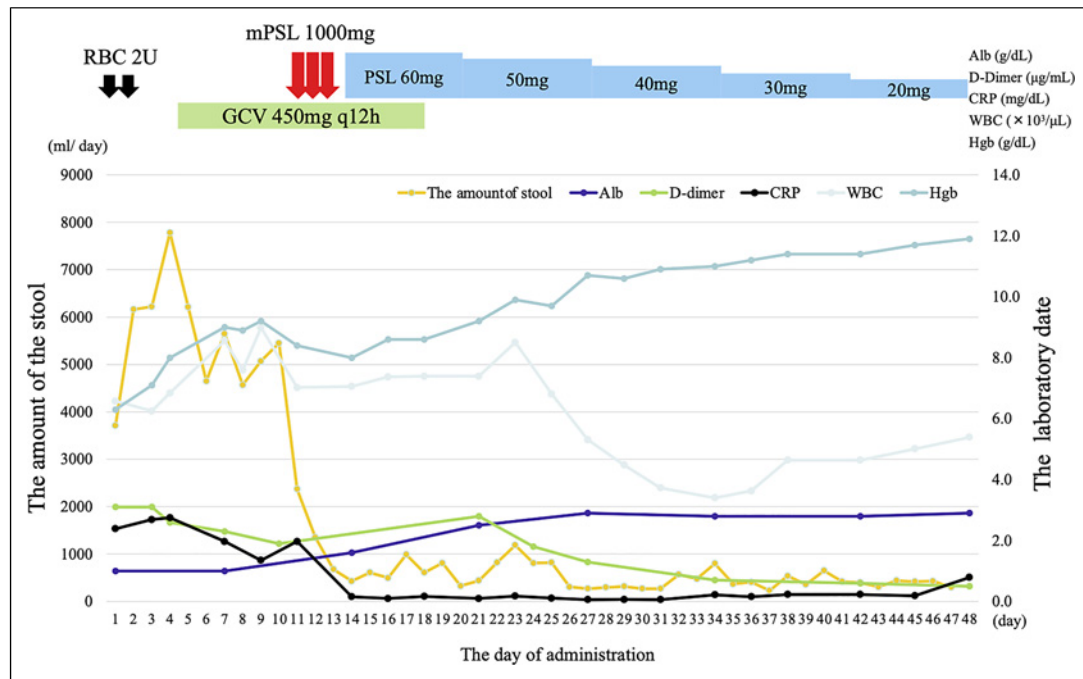


Fig. 2. Clinical course from administration day. Clinical course since transfer to our hospital, including treatment details, laboratory data (WBC, Hgb, Alb, CRP, D-dimer) changes, and stool volume. WBC, white blood cell; Hgb, hemoglobin; Alb, albumin; RBC, red blood cell concentrate; mPSL, methylprednisolone; GCV, ganciclovir; PSL, prednisolone.

reported recently [8–15]. We summarized literature review in December 2023, which searched PubMed with the key words “COVID-19” and “severe diarrhea.” A list of the reported cases, including the present case, is provided in Table 1. Among previously reported cases in which steroids were effective, there have been no detailed descriptions of the changes in endoscopic findings or clinical course. In case of severe diarrhea and extensive enterocolitis with elevated IL-6 levels, as observed in the present case, it is important to consider enterocolitis associated with COVID-19 and steroid administration. Endoscopic findings of COVID-19-related enterocolitis have been reported to mimic graft-versus-host disease, including edema, mucosal sloughing, and tortoiseshell pattern. In addition, COVID-19-related enterocolitis may be characterized by extensive edema, ulceration, and erosion throughout the small and large intestines.

Several hypotheses have been proposed regarding the cause of enterocolitis associated with COVID-19: (1) infection of the intestinal mucosa by SARS-CoV-2, (2) ischemic changes due to accelerated thrombus formation after viral infection, (3) changes in the intestinal microflora, (4) secondary infections by bacteria or viruses, and (5) abnormal immune responses after viral infection. In this case, 43 days passed between the onset of COVID-19 and the onset of diarrheal symptoms. Moreover, the PCR test for SARS-CoV-2 from the pharyngeal mucosa after the onset of diarrhea was negative. Therefore, GI mucosal damage caused directly by SARS-CoV-2 was unlikely. Yantiss et al. [10] reported three cases of intestinal abnormalities caused by COVID-19, with SARS-CoV-2 infection of the intestinal mucosa observed only in 1 patient with bleeding from the colon on day 5 after infection. In the other two cases of GI mucosal damage more than 10 days after infection, SARS-CoV-2 infection of the intestinal mucosa was not confirmed. Although SARS-CoV-2 may be directly involved in GI symptoms early after COVID-19 onset, its

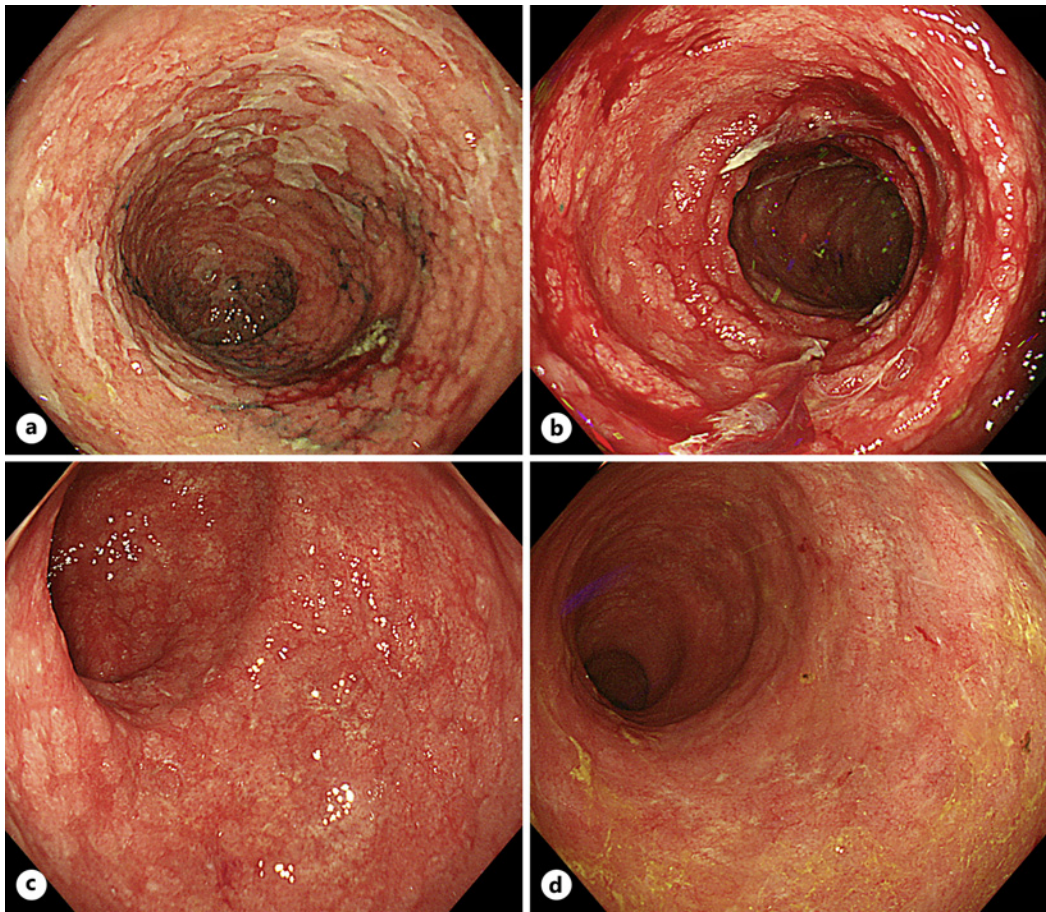


Fig. 3. Secular change of colonoscopic images. Secular changes in endoscopic images of the sigmoid colon. 2 (a), 18 (b), 30 (c), and 40 (d) days after transfer. Before the initiation of prednisolone treatment, the patient had extensive shallow ulcerations throughout the colonic mucosa (a). After the initiation of mPSL treatment, the ulceration disappeared, although it was susceptible to hemorrhage (b). Thereafter, the mucosal findings gradually improved (c), and the edema disappeared before the patient was transferred (d). mPSL, methylprednisolone.

involvement in delayed-onset symptoms is unlikely. In our report, thrombosis was less likely to be involved in the pathogenesis as the d-dimer levels remained mildly elevated after the patient was transferred to our department but then decreased spontaneously and eventually normalized. Reports from Europe indicate that endoscopic findings associated with COVID-19 often resemble those of ischemic enterocolitis [16]. However, most of them were diagnosed in the acute phase of COVID-19, and the endoscopic images in their reports differed from those in our case. Considering the extensive GI erosions/ulcerations and mucosal sloughing, the endoscopic image of the present case was similar to those of previous reports of enterocolitis associated with COVID-19 [8, 9, 11, 13, 15]. There have been recent reports of intestinal microbiota changes in patients with COVID-19. Zuo et al. [17] reported that intestinal microbiota changes in patients with COVID-19 include a decrease in commensal flora such as *Eubacterium ventriosum*, *Faecalibacterium prausnitzii*, *Roseburia*, and *Lachnospiraceae*, as well as an increase in opportunistic bacteria such as *Clostridium hathewayi*, *Actinomyces viscosus*, and *Bacteroides nordii*. Additionally, Shimizu et al. [14] reported dramatic changes in gut microbiota in patients with COVID-19-related massive diarrhea. Unfortunately, we could not extensively evaluate the intestinal

Table 1. Reported cases of severe diarrhea associated with COVID-19

Author, year	Age	Sex	Past medical history	ECMO	Duration after infection	Treatment	Outcome
Ozawa et al. [8], 2021	Unknown	Male	HT, hyperthyroidism Bronchial asthma	+	Unknown	PSL, IFX	Live
Inoue et al. [9], 2021	56	Male	Unknown	+	18 days	Antibiotics Somatostatin analog	Live
Yantiss et al. [10], 2022	88	Male	HT, prostate cancer	Unknown	12 days	Anti-diarrheal medicine, somatostatin analog PSL	Live
Yamakawa et al. [11], 2022	62	Male	HT, DM	+	36 days	PSL, IFX	Death
Shirohata et al. [12], 2022	59	Male	Unknown	+	40 days	Cholestyramine	Live
Masuda et al. [13], 2022	53	Male	HT	+	65 days	PSL, IFX	Death
Shimizu et al. [14], 2022	60	Male	Unknown	+	19 days	Anti-diarrheal medicine, synbiotics	Live
Hagiwara et al. [15], 2023	68	Male	HT, DM	+	29 days	GCV, plasma exchange	Death
Hagiwara et al. [15], 2023	71	Male	Prostate cancer	+	16 days	PSL, GCV, IFX	Death
Present case	50	Male	No medical history	+	43 days	GCV, PSL	Live

HT, hypertension; DM, diabetes mellitus; PSL, prednisolone; IFX, infliximab; GCV, ganciclovir; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation.

microbiota changes in this case; however, as the patient responded to PSL, intestinal microbiota changes were unlikely to be the primary pathophysiology. Initially, the patient tested positive for CMV antigen and was treated for CMV infection. Generally, patients with COVID-19 are often treated using systemic corticosteroids, which often results in immunosuppression. Therefore, patients with COVID-19 have been reported to be at risk of CMV infection [18]. Moreover, there have been several reported cases of enteritis due to CMV infection after COVID-19 [19, 20]. In case enteritis is suspected in patients with COVID-19 who have symptoms such as diarrhea or diagnostic imaging findings, it is important to consider CMV infection. However, the present case did not improve after ganciclovir administration and responded well to PSL, suggesting that an abnormal

immune response was most likely involved in the pathogenesis. Moreover, the elevated IL-6 in the patient further supports this hypothesis. Yamakawa et al. [10] reported high IL-6 expression in the terminal ileum and colon during the autopsy of a patient with massive diarrhea after COVID-19 treatment. IL-6 has been proposed to be the leading cause of excessive inflammation in patients with COVID-19, suggesting that COVID-19 may induce inflammation in the intestinal tract.

In recent years, multisystem inflammatory syndrome (MIS) has been reported [21]. Moreover, MIS has now been reported in adults (MIS-A) along with children (MIS-C) [21] with its characteristic clinical presentation. In patients with MIS, COVID-19 symptoms improve; however, multiple organ failure, Kawasaki disease-like and non-respiratory symptoms including shock, GI, dermal, and mucous membrane-related symptoms, and thrombocytopenia are often observed a few weeks later [22]. The Centers for Disease Control and Prevention for MIS-A included a fever of $\geq 38^{\circ}\text{C}$, which was not observed in our case. Therefore, the patient did not meet the diagnostic criteria for MIS-A. However, the patient had persistently high inflammatory response, including elevated CRP and IL-6 levels. Additionally, our patient showed gastrointestinal symptoms such as severe diarrhea. We think this case might have been GI MIS-A. All previously reported deaths were due to multiple organ failure; moreover, we believe that anti-inflammatory treatment with steroids should be promptly performed when the inflammation is confined to the gastrointestinal organs.

In conclusion, the prevalence of COVID-19-associated enterocolitis is low, and the pathogenesis of the disease remains unclear. Further investigation of the pathogenesis of the disease is needed through the accumulation and examination of cases. PSL administration should be considered in cases of post-COVID-19 symptoms of severe diarrhea due to a possible abnormal immune response related to COVID-19. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000539413>).

Acknowledgment

We would like to thank Editage (www.editage.com) for English language editing.

Statement of Ethics

This article does not contain any studies with human participants or animals performed by any of the authors. Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by any sponsor or funder.

Author Contributions

Akiyoshi Tsuboi, Shuya Shigenobu, Yuka Matsubara, Issei Hirata, Hidenori Tanaka, Ken Yamashita, Ryo Yuge, Yuji Urabe, Koji Arihiro, and Shiro Oka; Akiyoshi Tsuboi and Shiro Oka contributed to the conception and design of the study. The first draft of the manuscript was written by Akiyoshi Tsuboi. All authors commented on the previous versions of the manuscript and have read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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