Case Report

A case of massive refractory diarrhea in a patient with COVID-19

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Background: The new coronavirus disease (COVID-19) causes gastrointestinal symptoms as well as respiratory symptoms.

Case Presentation: A 60-year-old man was transferred with respiratory difficulty. He was diagnosed as having COVID-19 and was intubated and placed on mechanical ventilation. He suffered from diarrhea from day 12 and produced a maximum of approximately 6,384 mL/day of watery diarrhea on day 21. He required massive transfusion. Adsorbents and pectin-containing oligomeric formulas were administered, which decreased the amount of diarrhea. Fecal metagenomic analysis showed the proportions of the genera Enterococcus and Staphylococcus were the most dominate at the genus level. The proportion of Bacteroidetes was <1%. Thereafter, his diarrhea decreased to several times, and he was transferred to another ward on day 104.

Conclusion: Therapy for intestinal complications as well as that for pneumonia might be important in treating COVID-19.

Key words: COVID-19, diarrhea, gastroenterology and hepatology, intensive care unit, nutrition, sepsis/multiple organ failure

INTRODUCTION

SINCE AN OUTBREAK of pneumonia patients with the new coronavirus infection was reported in Wuhan in China in December 2019, there have been 5,954,311 cases of the new coronavirus infection and 26,756 deaths in Japan, according to the data from the Ministry of Health, Labour, and Welfare.[1]

The new coronavirus infection is caused by a new type of coronavirus (severe acute respiratory distress syndrome coronavirus 2 [SARS-CoV-2]) and is called COVID-19 (coronavirus disease 2019). The main clinical symptoms of the new coronavirus infection are fever, cough, anosmia, ageusia, upper respiratory tract symptoms, shortness of breath, fatigue, myalgia, headache, and confusion, but gastrointestinal symptoms also occurs in ~15% of patients.[2]

In this report, we describe a case of severe refractory diarrhea caused by the new coronavirus infection that was resolved by multidisciplinary treatment, along with changes in the gut microbiota.

This study was approved by the Ethics Committee and anonymized in accordance with the Personal Information Protection Law, and consent for publication has been obtained from the patient or his family.

CASE REPORT

THE PATIENT WAS a man in his 60s who had been suffering from fever and cough for a week before admission. His dyspnea worsened, so he called for an ambulance from home. On hospital arrival, his heart rate was 120/min, blood pressure 128/91 mm Hg, respiratory rate 28/min, and body temperature 38.8°C. Arterial blood gas analysis on 10 L of oxygen by reservoir mask showed pH 7.506, $PaCO_2$

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34.9 mm Hg, PaO_2 72.4 mm Hg, HCO_3^- 27.4 mmol/L, and BE 4.8 mmol/L. Computed tomography scanning showed ground-glass opacity in both lungs. Polymerase chain reaction (PCR) tests for SARS-CoV-2 on nasal wipe and aspirated sputum were both positive. His white blood cell count was 10,930/μL and C-reactive protein was 19.8 mg/dL. He was intubated and started on ventilatory management and treatment with antivirals, lopinavir and ritonavir (2 tablets two times daily), and antimicrobials, meropenem (MEPM) (3 g/day) and azithromycin (AZM) (500 mg/day) (Fig. 1.). The PaO_2/FIO_2 (P/F) ratio on the day of admission was 182, but on day 3, it decreased to 96, and his respiratory condition worsened, so extracorporeal membrane oxygenation (ECMO) was introduced. The culture result of aspirated sputum was negative, so the antimicrobials were de-escalated to ampicillin/sulbactam (AMPC/SBT) (9 g/day) from day 4, but as his respiratory condition worsened, MEPM was resumed, and levofloxacin (LVFX) (500 mg/day) and vancomycin (VCM) (1 g/day) were started from day 6 in consideration of severe infection. The interleukin 6 (IL-6) level at admission was as high as 2,080 pg/mL, so IL-6 receptor antibody (tocilizumab [TCZ], 8 mg/kg) was administered from day 7. Because his respiratory condition did not change, methylprednisolone (60 mg/day) was administered for 3 days from day 11. He developed diarrhea on day 12. Because the culture result of aspirated sputum was negative and diarrhea continued, the antimicrobial was de-escalated from MEPM to AMPC/SBT on day 14. Although *Clostridioides difficile* antigen and toxin were both negative, his diarrhea increased to 3,944 mL/day on day 18, so enteral administration of VCM was started, followed by metronidazole (MNZ) (1,500 mg/day). On day 20, despite the negative result of blood cytomegalovirus antigen (C7HRP), cytomegalovirus enteritis was suspected because of further increase of diarrhea to 5,010 mL/day, and ganciclovir (GCV) was started. He produced a maximum of 6,384 mL/day of watery diarrhea on day 21, requiring massive infusion and catecholamines to maintain circulatory dynamics. On the same day, we started astringents and adsorbents: albumin tannate (albumin tannate, 0.5 g three times daily) and natural aluminum silicate (ADSORBIN powder, 3.3 g three times daily). In addition, intermittent administration (half day) of pectin-containing oligomeric formulas (HINE E-GEL) at 20 mL/h was started through the gastric tube to gel the watery diarrhea, and *Bifidobacterium breve*, *Lactobacillus casei*, and galacto-oligosaccharide (Super Synbiotics) were started as synbiotics to stabilize the gut microbiota. The culture result of feces showed only *Candida* sp., and oral amphotericin B was also started. The amounts of diarrhea started to decrease from the next day and decreased to 1,735 mL/day on day 23, 2 days after the beginning of these treatments. Once albumin tannate and natural aluminum silicate were discontinued, diarrhea increased to 3,738 mL/day on day 24, but when immunoglobulin preparation was added and albumin tannate and natural aluminum silicate were resumed, it started to decrease again. After day 30, it was reduced to <1,000 mL/day. ECMO was removed on day 39.

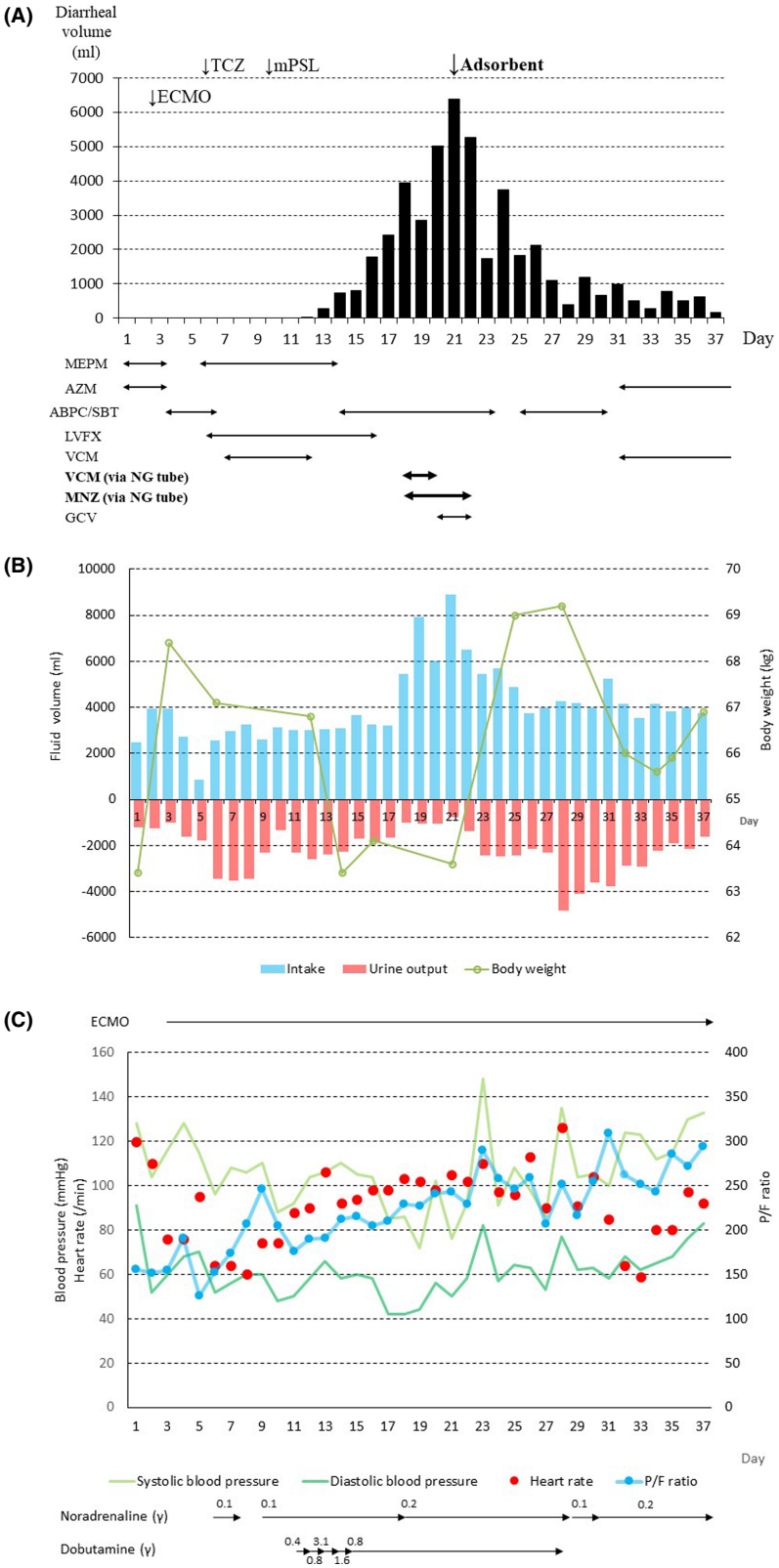
Fecal Gram stain[3] and culture were performed periodically, and fecal Gram stain showed either the single pattern or the depleted pattern, indicating the loss of diversity in the gut microbiota (Fig. 2). Fecal culture showed no increase in indigenous gut microbiota such as anaerobes, with only a change between mainly *Candida* sp., the genera of *Enterococcus*, coagulase-negative *Staphylococcus*, and *Klebsiella pneumoniae*. Diarrhea was reduced to several times a day, but remained, and he was transferred to the general ward on day 104.

Fecal metagenomic analysis[4] showed that the phylum Bacteroidetes is predominant in healthy individuals, but the phylum Firmicutes was predominant from admission (Fig. 3). After the onset of diarrhea, the phylum Firmicutes remained the most predominant. At the genus level, the phylum Firmicutes was occupied by the genera of *Enterococcus*, *Staphylococcus*, and the administered *Lactobacillus*. The genus *Bacteroides* in the phylum Bacteroidetes, which is one of the most predominant bacteria in healthy individuals, was ~1% on day 1 and was <1% on all subsequent days.

DISCUSSION

WE EXPERIENCED A case of refractory watery diarrhea of up to 6 L/day in a patient with severe COVID-19. The massive amounts of diarrhea were so critical that they affected the patient's circulatory dynamics and required immediate control. Although antibiotics-associated diarrhea is a possible cause of the diarrhea, the amounts of

Fig. 1. (A) Serial changes in the patient's fecal volume. The volume of feces rose to 6,384 mL/day on hospital day 21. TCZ, tocilizumab; mPSL, methylprednisolone; ECMO, extracorporeal membrane oxygenation; MEPM, meropenem; AZM, azithromycin; AMPC/SBT, ampicillin/sulbactam; LVFX, levofloxacin; VCM, vancomycin; NG, nasogastric; MNZ, metronidazole; GCV, ganciclovir. (B) Serial changes in the patient's fluid balance. (C) Serial changes in the patient's hemodynamic and respiratory status. The daily data were taken at 7 AM as representative.



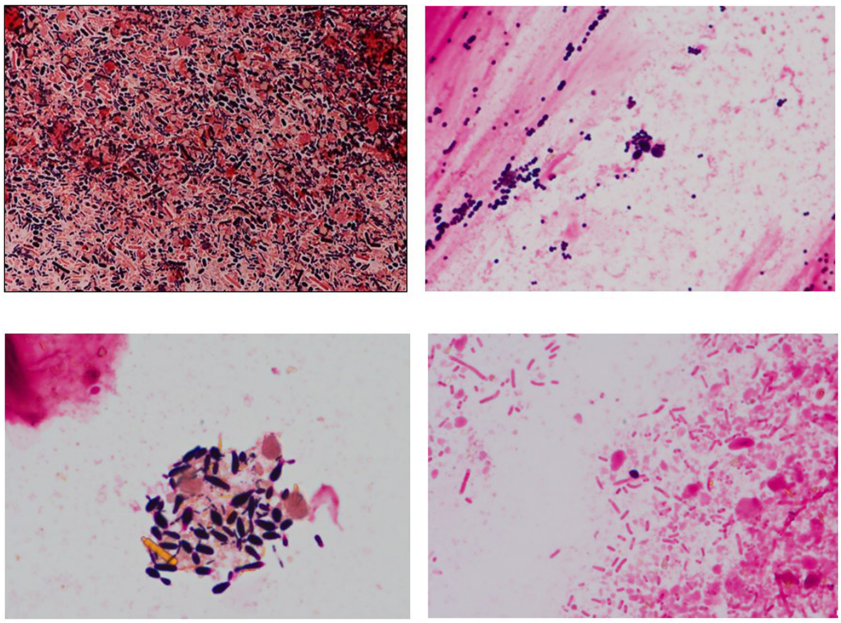


Fig. 2. Fecal Gram stain shows that simplified bacteria cover the field instead of normal bacteria. Upper left: healthy control. Upper right: *Enterococcus*. Lower left: fungi. Lower right: *Klebsiella pneumoniae*. The specimens were taken on day 46, day 21, and day 59.

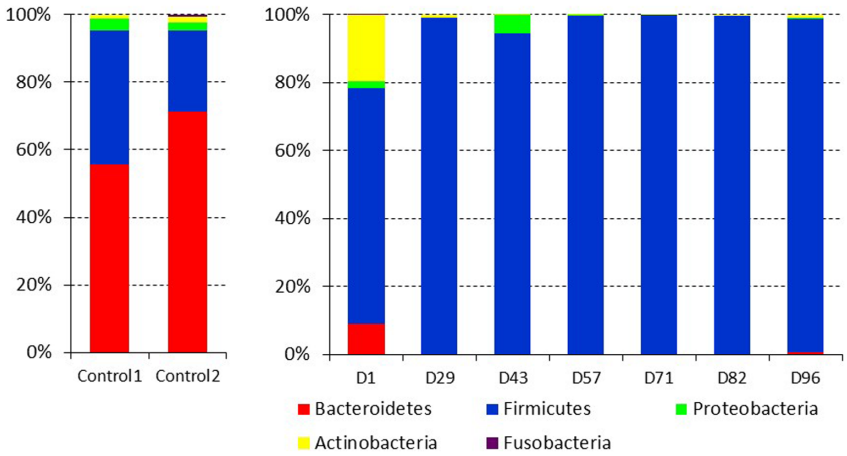


Fig. 3. Serial changes in the proportions of the phyla in the patient's fecal microbiota. Phylum Firmicutes continued to dominate in the feces during the patient's entire intensive care unit stay.

diarrhea in this case far exceeded that of usual critical illness, and we thought it necessary to consider the relationship between SARS-CoV-2 and the intestinal mucosa.

COVID-19 is thought to cause multiple organ failure from cytokine storm, but it has been reported to also affect the gastrointestinal tract.[2] Angiotensin-converting enzyme (ACE) 2, a receptor for SARS-CoV-2, is expressed not only in the lungs, but also in the small intestine and is involved in the regulation of amino acid absorption, among others. ACE2 knockout mice developed severe enteritis and diarrhea with changes in the gut microbiota, but did not suffer from enteritis after administration of tryptophan and nicotinamide.[5] It is known that severe diarrhea is a side effect of ACE inhibitors. In this case, we thought that the disruption of the gut microbiota by the administration of antimicrobials and the damage to the intestinal epithelium by SARS-CoV-2 might have led to the massive watery diarrhea. In a clinical study, fecal viral loads were detected[6] and digestive

histologic and immunofluorescent staining of ACE2 revealed gastrointestinal infection in patients with COVID-19.[7] The evaluation of intestine could be a next target to confirm gastrointestinal infection.

In general, the intestinal tract is an important target organ during invasion, and the intestinal dysfunction caused by inflammatory reactions because of infection or trauma is considered to play a central role in the progression of systemic inflammatory reactions and in the development of multiple organ failure as "the motor of critical illness." The most predominant bacteria in the gut microbiota of healthy individuals are obligatory anaerobes such as *Bacteroidaceae* and *Bifidobacterium*, but these bacteria are reduced in critically ill patients,[8] and disruption of the gut microbiota has been reported to be associated with bacteremia and prognosis.[9] In this case, during the first week after admission to the intensive care unit, the phylum Bacteroidetes, which accounts for ~50% of the bacteria in healthy individuals, was almost undetectable, and the genus *Enterococcus* in the phylum Firmicutes accounted for the majority in this case. The gut microbiota was disrupted, and this could be related to the inflammatory response from the intestinal tract to the whole body. In the gut microbiota of COVID-19 patients, the indigenous microbiota such as *Eubacterium ventriosum*, *Faecalibacterium prausnitzii*, *Roseburia*, and *Lachnospiraceae* decreased, and opportunistic bacteria such as *Clostridium hathewayi*, *Actinomyces viscosus*, and *Bacteroides nordii* increased.[10] In addition, SARS-CoV-2 has been detected in colorectal tissues and feces of COVID-19 patients, and it has been reported that there is a negative correlation between the genus *Bacteroides* and the amount of virus in feces. In the present case, although it is a matter of speculation, we can presume that the increased viral load of SARS-CoV-2 in the intestinal tract might have caused an inflammatory reaction in the intestinal tract, leading to a disruption of the gut microbiota such that the percentage of the genus *Bacteroides* became extremely low, resulting in refractory diarrhea. Colonoscopy for diagnosis and examination of the amount of virus in feces are future tasks.

For treatment, we used adsorbents and pectin-containing oligomeric formulas to prevent water loss from the body. Their effect was remarkable, with the amount of diarrhea decreasing to less than half within 48 h. As other treatments, synbiotics were used because of their ability to reconstruct the gut microbiota and decrease infectious complications such as diarrhea or ventilator-associated pneumonia,[11] but they could not improve the gut microbiota in the long term. Fecal microbiota transplantation has been considered as a future option as a means of reconstructing the gut microbiota in patients suffering from refractory diarrhea. In a case of diarrhea of >5 L/day because of multiple trauma, the diarrhea was reported to have disappeared within a few days after fecal microbiota transplantation,[12] and the gut microbiota improved. We used immunoglobulin therapy because the patient's IgG level was low, and there are reports of patients administered immunoglobulin preparation for refractory diarrhea.[13] Although the efficacy of each treatment is still unclear, future development of treatment methods is expected.

In this patient, COVID-19 might have contributed to the disruption of the gut microbiota and the development of massive diarrhea. It is important to consider intestinal therapy in future COVID-19 treatment.

CONCLUSION

WE EXPERIENCED A case of refractory massive diarrhea in a patient with severe COVID-19. Defecation management with a focus on adsorbents was effective for this patient's massive diarrhea. In the gut microbiota, the genus *Bacteroides* and other indigenous microbiota were decreased, and the genera *Enterococcus* and *Staphylococcus* were the most predominant. This suggests the importance of not only pneumonia treatment, but also intestinal therapy for severe COVID-19 cases.

DISCLOSURE

APPROVAL OF THE Research Protocol: This study was approved by the Ethics Committee and anonymized in accordance with the Personal Information Protection Law.

Informed Consent: Consent for publication has been obtained from the patient or his family.

Registry and the Registration No. of the Study/Trial: N/A.

Animal Studies: N/A.

Conflict of Interest: None declared.

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