Revista de Gastroenterología de México 87 (2022) 59–62

REVISTA DE GASTROENTEROLOGÍA DE MÉXICO

www.elsevier.es/rgmx

SPECIAL ARTICLE COVID19

Two consecutive attacks of diarrhea in 15 COVID-19 patients: An antibiotic-associated one following the viral one☆

R. Maslennikov[a,b,*], **V. Ivashkin**[a], **A. Ufimtseva**[a], **E. Poluektova**[a,b]

[a] *Department of Internal Medicine, Gastroenterology and Hepatology, Sechenov University, Moscow, Russian Federation*
[b] *Scientific Community for Clinical Study of the Human Microbiome Research, Moscow, Russian Federation*

Received 12 February 2021; accepted 15 June 2021

KEYWORDS
COVID-19;
Diarrhea

Abstract Of the 971 patients admitted to our Clinic with suspected COVID-19, 15 (1.5%) presented with two consecutive attacks of diarrhea. One of those patients (a 47-year-old woman) required admission to the intensive care unit and mechanical ventilation. She died on the 11th day of hospitalization (18th day of illness). The first attack of diarrhea in those patients occurred on the 6th (4th-7th) day of disease and lasted 3 (3-5) days. The second attack of diarrhea developed 11 (8-12) days after the initial onset of diarrhea. Despite the existing trend, the difference in the duration of the diarrhea and the maximum number of bowel movements per day between the first and second attacks was not statistically significant ($p = 0.130$; $p = 0.328$). There was no significant difference between the patients with a double attack of diarrhea and those with no diarrhea, regarding the results of the complete blood count, biochemical blood tests, and inflammation biomarkers.

PALABRAS CLAVE
COVID-19;
Diarrea

Dos ataques de diarrea consecutivos en 15 pacientes de COVID-19: uno asociado con antibióticos posterior a uno viral

Resumen De los 971 pacientes admitidos en nuestra clínica por sospecha de COVID-19, 15 (1.5%) presentaron dos ataques de diarrea consecutivos. Uno de dichos pacientes (una mujer de 47 años) requirió admisión a la unidad de cuidados intensivos y ventilación mecánica. Murió

☆ Please cite this article as: Maslennikov R, Ivashkin V, Ufimtseva A, Poluektova E. Dos ataques de diarrea consecutivos en 15 pacientes de COVID-19: uno asociado con antibióticos posterior a uno viral. Revista de Gastroenterología de México. 2022;87:59–62.

* Corresponding author at: Pogodinskaya str., 1, bld. 1, 119435, Moscow, Russian Federation. Tel.: +7-916-0825701; Fax: +7-499-2483533.
E-mail address: mmmm00@yandex.ru (R. Maslennikov).

el 11.o día de hospitalización (18 días de enfermedad). El primer ataque de diarrea en dichos pacientes ocurrió el 6.º (4.º-7.º) día de enfermedad, con una duración de 3 (3-5) días. El segundo ataque de diarrea se desarrolló 11 (8-12) días después del comienzo inicial de diarrea. A pesar de la tendencia existente, la diferencia en la duración de la diarrea y el número máximo de movimientos intestinales por día entre el primer y el segundo ataque no fue estadísticamente significativa (p = 0.130; p = 0.328). Tampoco existió diferencia significativa respecto a los resultados del conteo sanguíneo completo, las pruebas bioquímicas sanguíneas, ni los biomarcadores inflamatorios, entre los pacientes que presentaron un doble ataque de diarrea y los que no presentaron diarrea.

Introduction

The novel coronavirus infection (COVID-19) has become a new challenge of our time,[1] but not only as a disease of the respiratory system. Approximately 10% of COVID-19 patients present with diarrhea.[2,3] In addition, heavy use of antibiotics can lead to the development of antibiotic-associated diarrhea.[4] Our wish was to bring to your attention 15 cases of COVID-19 patients that presented with two consecutive attacks of diarrhea: antibiotic-associated diarrhea following coronavirus-induced diarrhea.

Materials and methods

A retrospective single-center study was conducted and included all the patients admitted to the Internal Diseases, Gastroenterology, and Hepatology Clinic of the Sechenov University, with suspected COVID-19, according to the World Health Organization guidelines,[5] from April to July 2020.

Diarrhea was defined as the presence of loose or watery stools, occurring more than 3 times a day. A second attack of diarrhea was defined as loose or watery stools occurring after at least 2 days of bowel movement normalization.

The data were presented as median values (interquartile range) and group comparisons were carried out using the Mann-Whitney U test.

Results

Of the 971 patients with suspected COVID-19 that were admitted to the Clinic,[5] 235 presented with diarrhea. Fifteen of those patients had two consecutive attacks of diarrhea. All patients received antibiotics. In addition, they received anticoagulants, glucocorticoids, hydroxychloroquine, and anticytokine drugs, according to indications and contraindications.

There were two-times more women than men (10/5), body mass index was 29.8 kg/m^2 (26.0-33.9), age was 64 years (49-69), and body temperature upon admission was 37.7 (37.2-38.3).

One of the patients that presented with a double diarrhea attack had been previously hospitalized 3 months earlier.

Another of those patients (a 47-year-old woman) was admitted to the intensive care unit and required mechanical ventilation. She died on the 11th day of hospitalization (18th day of illness).

The patients with the two attacks of diarrhea were in hospital for 15 days (13-20) and the total duration of the disease was 25 days (20-29).

The first attack of diarrhea developed before taking antibiotics, and the second one developed after antibiotic use, in all 15 patients (p < 0.001).

The first attack of diarrhea occurred on the 6th day (4th-7th) of disease and lasted 3 days (3-5). The maximum number of bowel movements was 3.5 per day (2-4.5). The initial diarrhea was self-limiting and did not require special treatment in most cases.

The second attack of diarrhea developed 11 days (8-12) from the onset of the first one (i.e., 5 days [4–11] after the end of the initial attack). It occurred on the 15th day (12th-19th) of disease and lasted 5 days (3-8). The maximum number of bowel movements was 4 per day (3-7). The second attack was treated with oral metronidazole (n = 7), oral vancomycin (n = 4), and the *Saccharomyces boulardii* probiotic (n = 11), in different combinations.

Despite the existing trend, the difference in the duration of the diarrhea and the maximum number of bowel movements per day between the first and second attacks did not reach statistical significance (p = 0.130; p = 0.328), perhaps due to the small number of cases.

The drugs utilized in the patients before the development of the second attack of diarrhea were: azithromycin (n = 13), oral and parenteral levofloxacin (n = 4 and n = 2, respectively), oral and parenteral moxifloxacin (n = 3 and n = 3, respectively), oral and parenteral amoxicillin/clavulanate (n = 4 and n = 2, respectively), meropenem (n = 2), ceftriaxone (n = 12), oral and parenteral clarithromycin (n = 1 and n = 1, respectively), josamycin (n = 1), hydroxychloroquine (n = 4), and parenteral dexamethasone (n = 10).

The test for *Clostridioides difficile* toxins was performed on 2 patients during the first attack of diarrhea (all results were negative) and on 4 patients during the second attack (all results were positive). Because intestinal infections of other etiologies are rarely detected in our practice due to high sanitary standards, testing for the presence

of other pathogens of infectious diarrhea was not carried out.

Colitis was detected with colonoscopy during the second attack of diarrhea in 3 patients: the entire colon was affected in 2 of them and the descending colon and sigmoid colon were affected in the other patient. Colon biopsy was not performed. All patients with colitis tested positive for *C. difficile* toxins and had severe diarrhea. The initial attack of diarrhea was not severe in any of the patients and the second attack was not severe in 12 patients, therefore colonoscopy was not performed on them.

COVID-19 symptoms in patients with a double attack of diarrhea included fever (n = 14), fatigue (n = 14), cough (n = 10), shortness of breath (n = 9), chest pain (n = 3), headache (n = 3), myalgia (n = 2), abdominal pain (n = 2), loss of taste (n = 2), loss of smell (n = 1), runny nose (n = 1), vomiting (n = 1), and anorexia (n = 1).

The chronic diseases present in the patients that developed two consecutive attacks of diarrhea were: cardiovascular disease (n = 9), respiratory disease (n = 2), liver disease (n = 1), and kidney disease (n = 3). Three of the patients presented with obesity, one patient presented with cancer, and 4 had diabetes. Five of the 15 patients with a double attack of diarrhea did not have chronic diseases.

There was no significant difference between the patients with a double attack and the patients with no diarrhea, regarding the results of the complete blood count, biochemical blood tests, and inflammation biomarkers.

The mortality of patients with a double attack of diarrhea (6.7%) did not differ significantly from the mortality of patients without diarrhea (3.8%; p = 0.596) or from the patients with one attack of diarrhea (4.5%; p = 0.707).

The patients with a double attack of diarrhea had no history of inflammatory bowel disease or irritable bowel syndrome and had no diarrhea after hospital discharge, during the 6 months of follow-up.

Discussion

Diarrhea is one of the manifestations of coronavirus (SARS-CoV-2) infection and can also be a complication of antibiotic treatment for mixed viral-bacterial pneumonia. Separating those types of diarrhea remains challenging. Diarrhea in COVID-19 can be divided into early diarrhea (which develops before hospitalization) and late diarrhea (which appears during hospitalization).[6,7] Moreover, in a study by Lin et al., late diarrhea developed almost exclusively in patients that were given antibiotics.[6] The incidence of late diarrhea was approximately 25% in the patients that received antibiotics and about 5% in those that did not. Therefore, we believe that in most cases, early (pre-hospitalization) diarrhea has a viral origin, whereas late (during hospitalization) diarrhea is antibiotic-associated. In our cases, late diarrhea developed after antibiotic use in all the cases, and *C. difficile* toxins were detected in all of the four patients tested.

The differential diagnosis of late diarrhea also included other infectious diarrheas, inflammatory bowel disease, and irritable bowel syndrome. The development of another type of infectious diarrhea during hospitalization at our clinic is extremely unlikely due to the existing high sanitary standards. Inflammatory bowel disease and irritable bowel syndrome are manifested by chronic diarrhea, but in our cases, the diarrhea was acute. There was also no history of those bowel diseases, nor were there any new attacks of diarrhea during the 6 months of follow-up, making inflammatory bowel disease and irritable bowel syndrome unlikely causes of diarrhea in our patients.

We present herein a case series of COVID-19 patients that had a double attack of diarrhea, in which the first attack developed before the patients received antibiotics, and the second attack developed after the patients started receiving antibiotics. Our observations provide evidence of the heterogeneity of diarrhea in COVID-19: the first attack can be interpreted as viral diarrhea, and the second as antibiotic-associated diarrhea.

The strength of our manuscript lies in the fact that it is the first to describe a case series on COVID-19 patients with a double attack of diarrhea. A limitation of our study is its small number of cases, as well as the low number of patients tested for the presence of *C. difficile* toxins. Further studies with a large number of such cases and *C. difficile* testing at each attack in all patients are needed, to confirm our study conclusions.

Ethical considerations

All procedures involving human participants were performed in accordance with the ethical standards of the institutional research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

The study was approved by the ethics committee of the Sechenov University.

Financial disclosure

No funding.

Conflict of interest

The authors declare that there is no conflict of interest.

References

1. Madabhavi I, Sarkar M, Kadakol N. COVID-19: a review. Monaldi Arch Chest Dis. 2020;90, http://dx.doi.org/10.4081/monaldi.2020.1298.
2. Tariq R, Saha S, Furqan F, et al. Prevalence and mortality of COVID-19 patients with gastrointestinal symptoms: a systematic review and meta-analysis. May Clin Proc. 2020;95:1632–48, http://dx.doi.org/10.1016/j.mayocp.2020.06.003.
3. Maslennikov R, Poluektova E, Ivashkin V, et al. Diarrhoea in adults with coronavirus disease—beyond incidence and mortality: a systematic review and meta-analysis. Infect Dis (Lond). 2021;53:348–60, http://dx.doi.org/10.1080/23744235.2021.1885733.
4. Mullish BH, Williams HR. Clostridium difficile infection and antibiotic-associated diarrhoea. Clin Med (Lond). 2018;18:237–41, http://dx.doi.org/10.7861/clinmedicine.18-3-237.

5. Clinical management of COVID-19. WHO/2019-nCoV/clinical/2020.5 Clinical management of COVID-19: interim guidance, 27 May 2020.(who.int).
6. Lin L, Jiang X, Zhang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut. 2020;69:997–1001, http://dx.doi.org/10.1136/gutjnl-2020-321013.
7. Zhang L, Han C, Zhang S, et al. Diarrhea and altered inflammatory cytokine pattern in severe coronavirus disease 2019: Impact on disease course and in-hospital mortality. J Gastroenterol Hepatol. 2021;36:421–9, http://dx.doi.org/10.1111/jgh.15166.