# Letter: Which 'C' is the Culprit? *Clostridioides difficile*, Cytomegalovirus or COVID-19 in a Patient with Acute Severe Ulcerative Colitis

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J Gastrointest Infect 2022;12:78–79.

Ulcerative colitis (UC) is a chronic disease with a relapsing-remitting course along with episodes of acute exacerbation. Infective conditions might mimic the flare of underlying disease. Patients with acute severe ulcerative colitis (ASUC) are prone to colectomy and mortality. Here, we present a case of UC with a flare of disease with concomitant infection of *Clostridioides difficile*, cytomegalovirus (CMV) virus, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.

A 38-year-old male, diagnosed with UC (Montreal Classification-E3 disease, extensive colitis) for 3 years, presented with a 15 days history of bloody diarrhea. The stool frequency was 12 episodes/day, with blood in all. He was also a known case of seizure disorder for the past 18 years and was on oral carbamazepine (600 mg per day). The last breakthrough seizure episode occurred 3 years ago. He had a history of admission as steroid unresponsive ASUC in 2019. He received intravenous cyclosporine induction at a 2 mg/kg/day dose, followed by 4 mg/kg/day oral cyclosporine for 4 months. He had an uneventful course since then. He was on maintenance of 5-aminosalicylic acid (4.8 g per day) with azathioprine (100 mg per day). He received the first dose of the coronavirus disease 2019 (COVID-19) vaccine in July 2021 and the second dose 4 months later. He was admitted after reverse-transcription polymerase chain reaction (RT-PCR) COVID-19 negative status as a part of admission screening protocol amid the pandemic. Because of the acute severe disease setting, he was started on intravenous methylprednisolone (60 mg per day) and anticoagulation. Sigmoidoscopy showed deep punched out ulcers with mucosal bleed (Mayo endoscopic score 3) (►**Fig. 1A**). On day 3, his stool frequency was 8 per day, with all stool episodes mixed with blood. He was counseled for biologicals because of nonresponse to steroids; however, he could not afford infliximab. He was initiated on intravenous cyclosporine (2 mg/kg/day infusion for 5 days) after neurology clearance for seizures. Stool *Clostridioides difficile* toxin assay (toxin A and B using an enzyme immunofluorescence assay) was sent on the day of admission. The report came positive on day 3. On the second day of cyclosporine induction, oral vancomycin was started at 750 mg/day in three divided doses. The histopathology of the rectal biopsy revealed florid activity in the form of mucodepletion, cryptitis, crypt distortion, crypt branching, along with occasional intranuclear inclusion of CMV (►**Fig. 1B**). After the initiation of cyclosporine, the patient had symptomatic improvement. The stool frequency declined to four episodes per day without any bleeding. On day 3 of cyclosporine injection, the patient developed fever and cough. Although the patient had COVID-19 RT-PCR negative at the time of admission on December 29, 2021, a repeat RT-PCR on January 6, 2022, came back positive. As the patient had mild SARS-CoV-2 infection, he was discharged with oral cyclosporine (4 mg/kg/day), azathioprine (50 mg/day), the tapering dose of steroids (40 mg/day), vancomycin (750 mg/day for 10 days), and cotrimoxazole (2 tabs/day). He is presently asymptomatic with a stool frequency of one per day.

Patients with UC are at risk of SARS-CoV-2 infection, but the risk is the same as that of the general population.[1] Initial reports suggested that cyclosporine could have an antiviral

**received**
January 18, 2022
**first decision**
January 30, 2022
**accepted after revision**
February 8, 2022

**DOI** https://doi.org/10.1055/s-0042-1757502.
**ISSN** 2277-5862.



Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

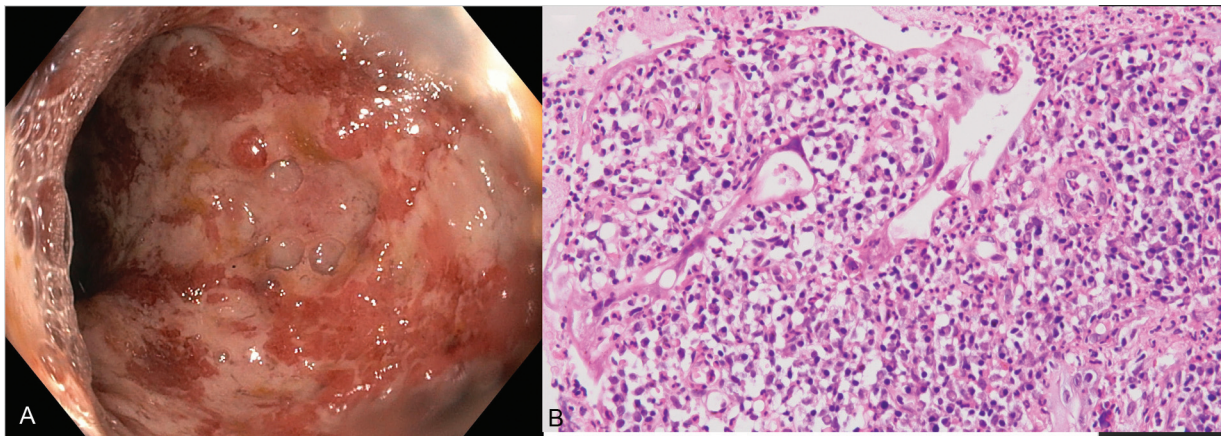


**Fig. 1** (**A**) Sigmoidoscopic image showing complete loss of vascular pattern and punched out ulcers with mucosal bleed. (**B**) Histopathological image showing multiple nucleocytomegalic epithelial and endothelial cells suggestive of cytomegalovirus inclusion (hematoxylin and eosin, 400 ×).

effect.[2] Cyclosporine is a calcineurin inhibitor that blocks the activation of T-cells via inhibition of interleukin-2. It thus prevents the development of the cytokine storm in severe COVID-19.[3] Tacrolimus has also been used successfully for the induction of remission in ASUC co-existing with severe SARS-CoV-2 pneumonia.[4] Cyclosporine probably might have a dual benefit in the treatment of ASUC as well as COVID-19. Our patient had a mild SARS-CoV-2 infection as he was vaccinated or probably due to a mild variant (omicron) prevalent or could be due to the use of cyclosporine. However, more data are needed regarding the potential use of cyclosporine in this setting. The impact of CMV infection in the course of UC has perplexed gastroenterologists. Various studies have suggested different threshold levels for tissue DNA-PCR, the number of inclusion bodies on hematoxylin and eosin stain, and tissue immunohistochemistry to differentiate CMV colitis from CMV just as a bystander.[5,6] As our index patient had positive immunoglobulin G CMV serology and negative serum CMV-DNA by nested PCR with few inclusion bodies in the colonic tissue, this could probably be an innocent bystander.

Infliximab was the first choice for induction in our patient. We had to make a difficult decision to use cyclosporine for induction due to cost concerns. As the patient was previously managed with cyclosporine and had no breakthrough seizure since the last admission, we used cyclosporine to induce remission. We report this case as it was a diagnostic dilemma with infections of CMV, *Clostridioides difficile,* and COVID-19 in UC and had a favorable outcome.

### Ethical Statement
Informed consent to publish obtained.

### Author Contributions
A.C.: Patient care, manuscript writing, D.J.: Patient care, manuscript writing, S.M.: Histological examination, A.J.: Patient care, manuscript writing, editing and final Draft. All authors approved the final version.

### Data Availability Statement
The relevant data are provided in the manuscript.

### Funding
None.

### Conflict of Interest
None declared.

### Acknowledgments
None.

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