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Case report

Cytomegalovirus Enterocolitis secondary to experimental COVID-19 therapy

Will R. Geisen[a,*], Justin Berger[a], Chelsea Schwartz[a], Abhimanyu Reddy[a], Balaj Rai[a], George Wadih[a], Joshua Peck[b]

[a] The Christ Hospital, Department of Pathology, Cincinnati, OH, United States
[b] Ohio Gastroenterology and Liver Institute, Cincinnati, OH, United States

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ABSTRACT

The novel coronavirus-2019 (COVID-19) has caused a global pandemic of historical proportions, infecting millions of people worldwide. Due to its high mortality rate and a paucity of clinical data, experimental therapies have been utilized with uncertain success and, unfortunately, poor outcomes. We describe a gentleman who was treated with experimental therapies and subsequently developed cytomegalovirus colitis and hypovolemic shock. Additionally, this case validates colonoscopy as a mode to rule out concurrent infectious etiologies causing diarrhea in COVID-19-positive patients.

Introduction

The novel 2019 coronavirus (COVID-19), a form of severe acute respiratory syndrome (SARS-CoV-2), has caused a pandemic of historical proportions. As of this publication, 16.7 million people have been diagnosed worldwide with 660,792 deaths reported. Approximately 10–15 % of these patients develop respiratory distress requiring hospitalization and, often, ICU admission [1,2]. Due to its worldwide distribution, a paucity of clinical trial data, and a high mortality rate, the COVID pandemic has led to widespread implementation of experimental therapies with varying levels of success and, in some instances, poor outcomes [3–5]. We present a patient who was treated with experimental therapies and subsequently developed severe gastrointestinal pathology that was diagnosed by colonoscopy.

Case report

A 68-year-old Caucasian male with medical history of hypertension and glaucoma presented with nausea, emesis, and fevers of 1-week duration. In the emergency department he became increasingly hypoxic and required 4 L of supplemental oxygen, warranting chest radiography. Chest x-ray demonstrated bilateral opacities concerning for atypical pneumonia and patient was started on cefepime, vancomycin, and azithromycin. Respiratory polymerase chain reaction (PCR) was positive for *Streptococcus* and *Staphylococcus* species and nasopharyngeal swab for SARS-CoV-2 was obtained prior to transfer to the Intensive Care Unit (ICU). The patient developed acute respiratory distress syndrome (ARDS) requiring intubation, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO). Computed tomography (CT) of the chest/abdomen/pelvis showed extensive ground glass opacities, pelvic ascites, and no intracolonic abnormalities. Six days after initial presentation, Coronavirus PCR resulted positive.

While awaiting confirmatory testing for SARS-CoV-2, the patient received five doses of hydroxychloroquine per experimental protocols. On day seven of admission, the patient received one dose of tocilizumab, an interleukin-6 (IL-6) inhibitor approved for giant cell arteritis. In addition, the patient received a ten-day course of remdesivir, an anti-viral agent with noted efficacy against RNA viruses.

In the ICU, the patient developed high-output diarrhea (2–4 liters daily) and hypovolemic shock. *Clostridioides difficile* toxin was negative on three separate occasions during his admission. GI panel polymerase chain reaction (PCR) for bacterial, viral, fungal, and protozoan causes of infectious diarrhea were also found to be negative. Gastroenterology was consulted and added octreotide, cholestyramine, atropine/diphenoxylate, and probiotics without significant improvement. CT of the abdomen and pelvis showed

* Corresponding author at: The Christ Hospital, Department of Internal Medicine, 2139 Auburn Avenue, Cincinnati, OH, 45219, United States.
E-mail address: will.geisen@gmail.com (W.R. Geisen).

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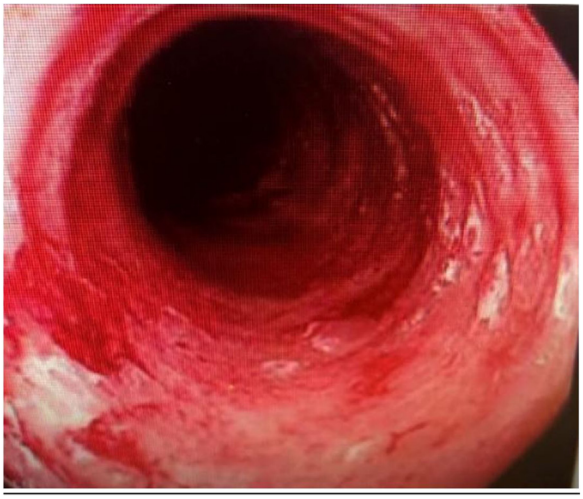

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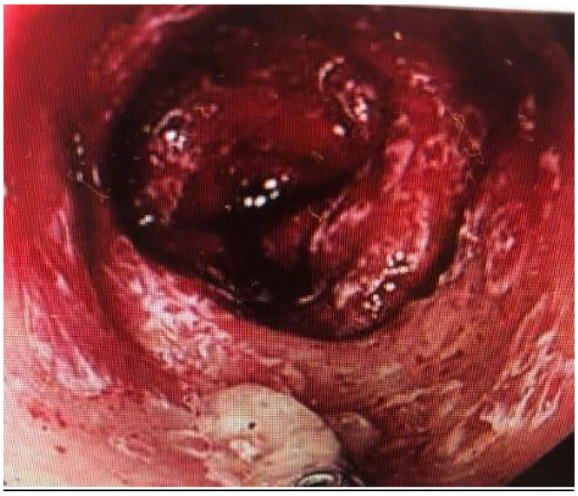

Fig. 1. a, b: Colonoscopy showing mucosal ulcerations and extensive inflammation through the colon. Lesions were biopsied and pathology/staining indicated CMV colitis.

extensive bowel wall thickening of the colon and distal ileum with rectal sparing.

Etiologies of infectious colitis, including cytomegalovirus (CMV), were entertained but initial DNA PCR were negative. Two weeks later, as the patient continued to have high output stools, CMV IgG and IgM were tested and demonstrated elevated IgG (1.50) and undetectable IgM. CMV quantitative PCR was highly elevated (55,937 IU/mL) indicating viremia and the patient was started on intravenous ganciclovir. Colonoscopy yielded multiple raised plaques within the terminal ileum and pan-colonic ulcerations that were biopsied and clipped (Fig. 1a, b). The obtained pathology showed focal glandular atypia, pseudostratification of enlarged nuclei, and inclusion bodies with positive immunohistochemical staining for CMV (Fig. 2a, b).

Discussion

The management of SARS-CoV-2 has included the use of many experimental therapies, including hydroxychloroquine, tocilizumab, and remdesivir. Several of these agents, specifically those approved for rheumatologic disorders, result in an

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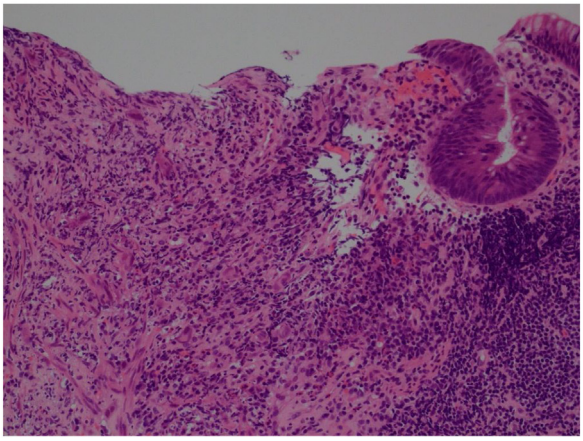

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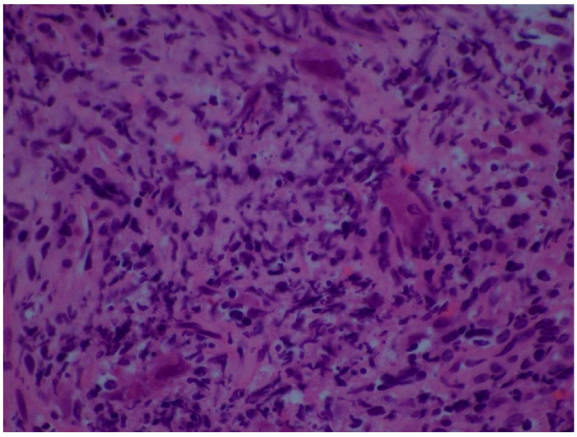

Fig. 2. a, b: Pathology obtained from colonic biopsies showing atypical nuclei and "owl's eye" inclusion bodies consistent with cytomegalovirus (CMV) infection.

immunocompromised state. Hydroxychloroquine has been shown to inhibit toll-like receptor pathways, thus dampening antigen presenting cells from activating inflammatory processes [6]. IL-6 is heavily involved in B-cell maturation into antibody producing cells and *in vivo* data from patients taking tocilizumab has noted a significant decrease the production of IgA/IgG [7]. These reductions in immunocompetency, especially IgA/IgG which are heavily involved in the protection of mucosal barriers, make the gastrointestinal tract vulnerable to opportunistic infections.

While anecdotal studies have led to the widespread use of experimental therapies [3,4], more comprehensive studies analysis have shown that these agents may cause increased mortality [5]. Additionally, studies have shown a significant alteration of gut microbiome and increased rates of *C. difficile* in COVID-19 patients, most presumably from immunomodulating therapies [6,8]. It is difficult to extrapolate the effect that COVID-19 will have on the field of gastroenterology, but one can assume that a rise in prevalence of infectious diarrhea is likely. This case exemplifies the notion that unproven therapies can lead to severe disease, including CMV colitis.

Of note, the presence of gastrointestinal symptoms, specifically diarrhea, have been widely reported in patients with COVID-19 [9,10]. A survey of 2506 patients with SARS-CoV-2 infection found that 5.8 % (145/2506) experienced diarrhea as a presenting symptom [9]. Because the virus attaches to and enters cells through angiotensin-converting enzyme 2 (ACE2), which has significantly higher expression in the small intestine than the lungs, it is believed that the gastrointestinal tract may play a key

role in the infectivity of COVID-19 [10]. Some speculate that viral invasion through the intestinal mucosa and the ensuing inflammation cause diarrhea in these patients [9,10].

However, while diarrhea may be a common symptom in early COVID-19 disease, this case illustrates that there is a role for colonoscopy to exclude concurrent infection in these patients. Colonic biopsy of the of inflamed lesions with hematoxylin and eosin (H&E) staining and immunohistochemistry is highly specific (92–99 %) for CMV and necessary to definitively diagnose CMV colitis [11]. With immunomodulating therapies being used in experimental protocols and clinical trials for SARS-CoV-2 infection, colonoscopy is vital to diagnose gastrointestinal opportunistic infections that are associated with these treatment modalities.

Author statement

The report describes a patient with SARS-CoV-2 pneumonia who was treated with experimental immunomodulating therapies and, subsequently, developed cytomegalovirus (CMV) colitis. Our manuscript stresses the potential dangers of experimental therapies in lieu of clinical trial data. It also emphasizes the role of colonoscopy in the evaluation of patients with infectious diarrhea secondary to COVID-19 and its management.

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Disclosures

None.

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