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Case Report

Age can be a Problem: *Clostridium difficile* and Cytomegalovirus Colitis Coinfection in an Immunocompetent 90-year-old Patient☆

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ABSTRACT

Clostridium difficile colitis and cytomegalovirus colitis coinfection has been documented in immunocompromised patients. However, this kind of coinfection has rarely been reported in immunocompetent patients. We present a 90-year-old, critically ill, immunocompetent patient, who had a *C. difficile* and cytomegalovirus colitis coinfection. Although the common risk factors of both types of colitis are well known, clinical physicians still need to be alert to this coinfection because severe complications of CMV colitis have been reported previously. Physicians should be more aggressive in the management of elderly immunocompetent patients with refractory symptoms of colitis.

1. Introduction

Immunosuppression is a risk factor for both *Clostridium difficile* colitis and cytomegalovirus (CMV) infection[1,2]. Immunocompetent patients are also at risk of developing these diseases, especially those who are elderly or critically ill[1,2]. CMV colitis superimposed on *C. difficile* colitis in immunocompromised hosts such as solid organ transplant recipients has been reported[3]. However, *C. difficile*-CMV colitis coinfection, which was first reported in 1992, is rare in immunocompetent patients[4]. Herein, we report an elderly immunocompetent patient with *C. difficile*-CMV colitis coinfection.

2. Case report

A 90-year-old male, who had a stroke 10 years ago and had been under chronic bedridden status, lived in a nursing home facility. He initially had pneumonia with respiratory failure and was admitted to an intensive care unit. He had been treated for pneumonia with multiple courses of antibiotics for 2 weeks. However, bloody diarrhea and poor digestion developed and a computed tomography of the abdomen showed thickening of the wall of the descending colon. The result of an enzyme immunoassay was positive for stool *C. difficile* toxin. The patient was given oral metronidazole at 500 mg three times per day for 8 days, but the diarrhea was only partially relieved. Sigmoidoscopy was performed and was advanced to the distal descending colon, where multiple ulcers with inflammatory changes were found (Fig. 1). Sigmoidoscopic biopsy over the ulcerative area was performed. Pathological finding for CMV immunohistochemistry stain was positive with presentation of typical intranuclear inclusions (Fig. 2). We prescribed intravenous ganciclovir at 5 mg/kg every 12 hours and kept the treatment course for pseudomembranous colitis because of refractory diarrhea. CMV quantitative blood polymerase chain reaction (PCR) performed 4 days after initiation of treatment with ganciclovir, revealed < 333 copies/mL. *human immunodeficiency virus* serology test was nonreactive and antinuclear antibody titer was insignificant. The patient was not exposed to any corticosteroids during this course of treatment. His symptoms of poor digestion and diarrhea gradually improved 1 week later after ganciclovir was added. When he finished the 2-week course of oral vancomycin and intravenous ganciclovir, the symptoms of diarrhea and digestion had improved greatly. However, the patient accepted a tracheostomy because of difficulty in weaning from mechanical ventilation. He was later transferred to a chronic respiratory care ward for long-term care.

☆ Conflicts of interest: We certify that all my affiliations with or financial involvement in, within the past 5 years and foreseeable future, any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript are completely disclosed (e.g., employment, consultancies, honoraria, stock ownership or options, expert testimony, grants, or patents received or pending, and royalties).

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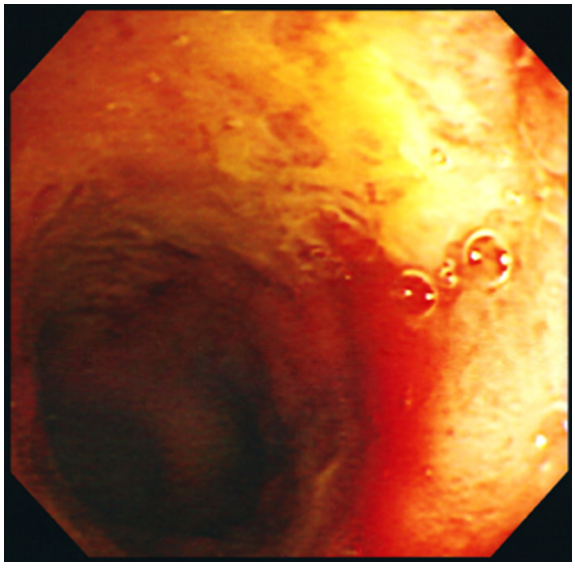

Fig. 1. Erythematous colonic mucosa with focal ulcer and hemorrhage in the sigmoid colon.

3. Discussion

Risk factors for *C. difficile* colitis and CMV colitis, including immunosuppression, older age, critically ill conditions, inflammatory bowel disease, postsurgical state, and high disease severity, have been mentioned in several studies[1,2,5–7]. The universal symptoms of both types of colitis are diarrhea, fever, and abdominal pain. Moreover, bloody diarrhea may be a bothersome symptom[5,8]. Although *C. difficile* colitis is generally not difficult to treat, drug resistant pathogens may cause severe complications, especially when there are widespread regional outbreaks associated with a previously uncommon hypervirulent strain of *C. difficile*.[1]

Alkhatib et al[9] reported an immunocompetent case of resistant *C. difficile* colitis and CMV colitis coinfection and they first proposed the term "triple C disease". A case of a young male patient was documented in Singapore[10]. Another report presented a 78-year-old woman who suffered from the coinfection with recovery to baseline health status after serial antibiotics, antiviral treatment,

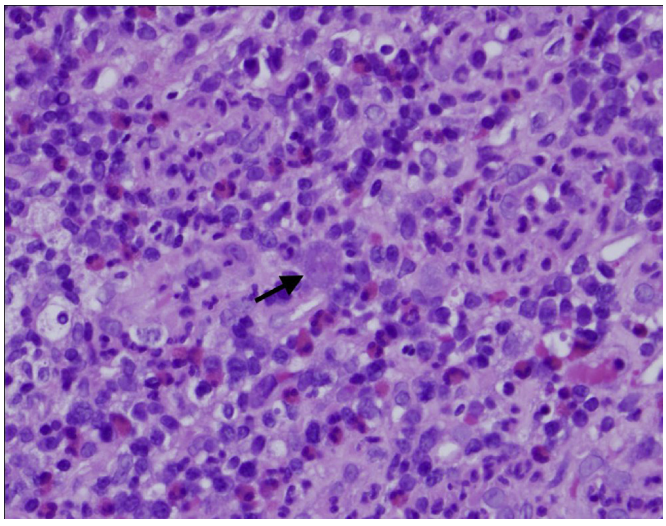

Fig. 2. Hematoxylin and eosin stain showing a typical intranuclear inclusion body.

Table 1
Cases of *Clostridium difficile* colitis and cytomegalovirus (CMV) colitis coinfection in immunocompetent hosts published in the literature.

Study	Age/sex	Diagnosis of *C. difficile* colitis	*C. difficile* treatment	Diagnosis of CMV colitis	CMV treatment	1st colitis diagnosed	Delayed treatment of the 2nd pathogen	Outcome
Jawad[4] 1992	83/female	Diarrhea + positive stool culture	Vancomycin	Biopsy	Ganciclovir	*C. difficile* colitis	NA	Death
Alkhatib et al[9] 2009	81/male	Diarrhea + positive *Clostridium* toxin	Metronidazole/vancomycin	PCR plus biopsy	Ganciclovir	*C. difficile* colitis	NA	Recovery
Momin et al[10] 2011	29/male	Diarrhea + direct colonscopy finding	Metronidazole	Biopsy	Ganciclovir for 14 days	*C. difficile* colitis	NA	Death due to pneumonia
Kurtz et al[11] 2012	78/female	Diarrhea + positive *Clostridium* PCR	Metronidazole/vancomycin/ fidaxomicin/stool transplant	Biopsy	Ganciclovir + total colectomy + 6-week oral valganciclovir	*C. difficile* colitis	NA	Recovery to baseline health status
This study	90/male	Diarrhea + positive *Clostridium* toxin	Metronidazole/vancomycin	PCR plus biopsy	Ganciclovir for 14 d	*C. difficile* colitis	14 days	Recovery

CMV = cytomegalovirus; PCR = polymerase chain reaction assay; NA = not available.

and total colectomy[11]. CMV infection in immunocompetent patients was previously thought to be rare and these patients were considered to have a benign course. In the literature, *C. difficile* colitis and CMV colitis coinfection in immunocompromised patients has been well documented[3], but cases of immunocompetent patients are very rare. To our knowledge, our case is the oldest one among the limitedly number of immunocompetent cases with coinfection reported in the literature (Table 1). In addition to the aforementioned young patient, another patient reported in the literature was 81 years old. It is well known that this coinfection is more common in immunocompromised patients. However, old age might be the key reason to explain why this coinfection occurs in immunocompetent patients.

Previous case reports did not mention the delay duration (Table 1), but we delayed treatment of the CMV pathogen for 14 days. It seems that the diagnosis of CMV colitis is usually delayed after *C. difficile* colitis has been diagnosed. This is probably because clinical physicians are less alert to CMV infection in immunocompetent patients. The young immunocompetent patient in Singapore died of multiple organ failure caused by multiple resistant pathogens[10]. Early diagnosis of the superimposed CMV infection might shorten the hospital course and lessen the possibility of a potentially lethal nosocomial infection.

Although the CMV quantitative blood PCR of our patient was not high, the data might be influenced by ganciclovir treatment because the decline of the viral load in the blood after intravenous ganciclovir therapy may be quick[12]. Moreover, detection of CMV by PCR alone is insufficient for the diagnosis of CMV gastrointestinal disease[13]. Accordingly, the utility of a serology test is limited in immunocompetent patients because of the requirement for paired serum samples and longer detectable period of CMV-specific immunoglobulin M autoantibodies after the onset of symptoms[14].

Clinical physicians began to pay attention to less common problems such as CMV infection when clinical symptoms of *C. difficile* colitis did not improve after treatment. Although previous studies could not prove that antiviral treatment is effective in immunocompetent patients with severe CMV infections[15], timely treatment might be helpful in the improvement of symptoms and outcome, as shown in a previously published case in 2009[9] and the current case. It became clear that prolonged hospital stays or higher risks of severe life-threatening complications of CMV infection in immunocompetent patients are not as rare as previously thought[15].

Previous studies[15,16] implied a cytokine cascade may increase the potential to reactivate the latent CMV infection in patients with inflammatory bowel disease. As for the reason of *C. difficile* colitis preceding CMV colitis, the cytokines induced by *C. difficile* colitis may play an important role even though the interaction is not yet clear. This may explain why CMV infection developed after *C. difficile* colitis in our case.

In conclusion, clinical physicians should be alert to the possibility of CMV coinfection, especially when an elderly and critically ill patient has refractory or recurrent symptoms of *C. difficile* colitis. Early endoscopic study might be helpful to differentiate disease or to evaluate disease severity. Prompt antiviral treatment after diagnosis might play a role in improvement of symptoms and outcome.

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