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A rare case intractable diarrhea secondary to *Clostridium difficile* and cytomegalovirus coinfection

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 63
Final Diagnosis: Cytomegalo virus (CMV) infection
Symptoms: Diarrhea
Medication: —
Clinical Procedure: —
Specialty: Infectious Diseases

Objective: Unusual clinical course

Background: Coinfection with cytomegalovirus in a patient with *Clostridium difficile* persistent diarrhea and colitis can lead to a delay in diagnosis and treatment.

Case Report: A 63-year-old man with squamous cell carcinoma of the lower lip, status post surgical resection and currently on chemoradiation presented with intractable diarrhea and abdominal pain. Initial workup showed *Clostridium difficile* diarrhea with pancolitis. Diarrhea persisted despite being on antibiotics and bacteriological cure for *C. difficile*. Further noninvasive work up revealed associated cytomegalovirus infection, and patient had a dramatic response to ganciclovir without any relapse.

Conclusions: Physicians should be cognizant about other causes of diarrhea and colitis in immunocompromised patient when treatment for primary diagnosis fails to resolve their symptoms.

Key words: cytomegalovirus • *Clostridium difficile* • pancolitis • coinfection • intractable diarrhea

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Background

Coinfection with cytomegalovirus and *C. difficile* is rarely reported in literature and when present, is often a diagnostic challenge and has a high mortality rate [1]. Most of the reported cases are in transplant patients who were on immunosuppressants. Most cases of *C. difficile* colitis responds to oral Vancomycin and or IV metronidazole. Persistence of symptoms despite being on optimal treatment regimen warrants workup for other causes. CMV infection can occur in a patient with *C. difficile*, either as a coexistent or secondary to disruption of the colonic mucosa following the latter infection. Since therapeutic approach is entirely different, early diagnosis with high clinical suspicion is warranted in these cases. We report the case of a *C. difficile*, CMV coinfection presenting as pancolitis which was managed successfully by a conservative approach.

Case Report

Our patient is a 63-year-old man admitted with episodes of nausea, vomiting and non-bloody foul smelling diarrhea for approximately 2 weeks and had been treated symptomatically. Patient denies any history of similar illness in the past. He also denied any recent sick contacts, recent travel or new foods or change in medications.

His past medical history is significant for resection of lower lip squamous cell carcinoma Stage T4 N1, was intolerant to cetuximab, an epidermal growth factor receptor (EGFR) inhibitor, currently on Oxyplatin and radiation therapy. He had a G-tube for tube feeds following surgical intervention for his squamous cell carcinoma with glossectomy, bilateral neck dissection and mandibular reconstruction.

His vitals on admission to the Emergency department were a temperature of 101.5° Farenheit (38.6°C), heart rate 110/minute, and a blood pressure of 90/60 mm of Hg. General examination findings at the time of admission revealed a chronically ill appearing, severely malnourished man of short stature, with a body mass index (BMI) of 17.7 Kg/m^2, who is alert and awake, not in any distress. Positive physical examination findings included healed surgical scars on the face and vague diffuse abdominal tenderness on palpation. Bowel sounds were hyperactive and rectal tone was intact.

Initial blood workup showed white blood cell count of 14.2×10^9/L, hemoglobin 12 g/dL, hematocrit 37.5%, platelets 314×10^9/L. Blood chemistries were within normal limits other than elevated venous lactate of 4.5 mg/dL. His serum albumin on admission was 1.2 gm/dL. In view of the clinical and laboratory findings suggestive of sepsis, patient was started on fluid resuscitation with normal saline and was started on broad spectrum antibiotics. Initial stool studies showed plenty of WBC's and a positive guaiac test. Later his stool *Clostridium difficile* toxin by polymerase chain reaction (PCR) came back positive for NAP1 strain. Stool studies were negative for ova, parasites, Salmonella, Shigella and Campylobacter jejuni. After discontinuing other antibiotics, he was started on vancomycin solution at 250 mg every 6 hours. He continued to have low grade fevers with tachycardia and elevated white cell count on peripheral blood. Work up for other source of infections including chest x-rays, blood and urine cultures came back negative. Computerized tomography (CT) of Abdomen and Pelvis with contrast showed findings of severe diffuse pancolitis (Figure 1A, 1B). Eventually, his sepsis resolved but he continued to have diarrhea. We increased the dose of his oral vancomycin to 500 mg every 6 hours via G tube. Despite being on this regimen for more than 7 days, patient had persistent watery diarrheas and elevated leukocytosis of up to 28×10^9/L. Hence he was started on IV metronidazole and vancomycin retention enemas and later Fidaxomicin with no satisfactory clinical response.

At this point stool *Clostridium difficile* by PCR was rechecked and it came back negative. While looking for other potential causes, including viral etiologies, his CMV PCR in stool (5000 IU/mL) and whole blood (3000 IU/mL) were significantly elevated. Patient denied any history of CMV associated illness in the past. Hence the possibility of associated CMV colitis was considered. Colonoscopy and biopsy were planned but was deferred given his severe diffuse pancolitis on imaging studies and severe debility. Also, patient's family was also reluctant to proceed with any invasive procedures given his poor general condition and persistent diarrhea. It was decided to start him empirically on Valganciclovir via G-tube. He had rapid and significant response to Valganciclovir in 48–72 hours of treatment with complete resolution of diarrhea and leukocytosis in 4–5 days after initiation of treatment. Patient started tolerating his tube feeds and was discharged to a skilled nursing facility for rehabilitation with Infectious disease follow up. He was maintained on a tapering dose of oral vancomycin and on Valganciclovir 900 mg q12h, for a total of 4 weeks. At 3 months of follow up, patient remained asymptomatic, with resolution of symptoms of viremia.

Discussion

Infection with *Clostridium difficile* has become more challenging because of the increasing incidence, disease severity with complications as well as high rate of recurrence. With the emergence of more virulent strains of *C. difficile* like B1/NAP1/027, the disease outcome has become more worse [2]. Most infections with *C. difficile* respond to vancomycin or metronidazole and absence of clinical improvement to these regimens warrants a search for alternative diagnosis [3]. The chances of

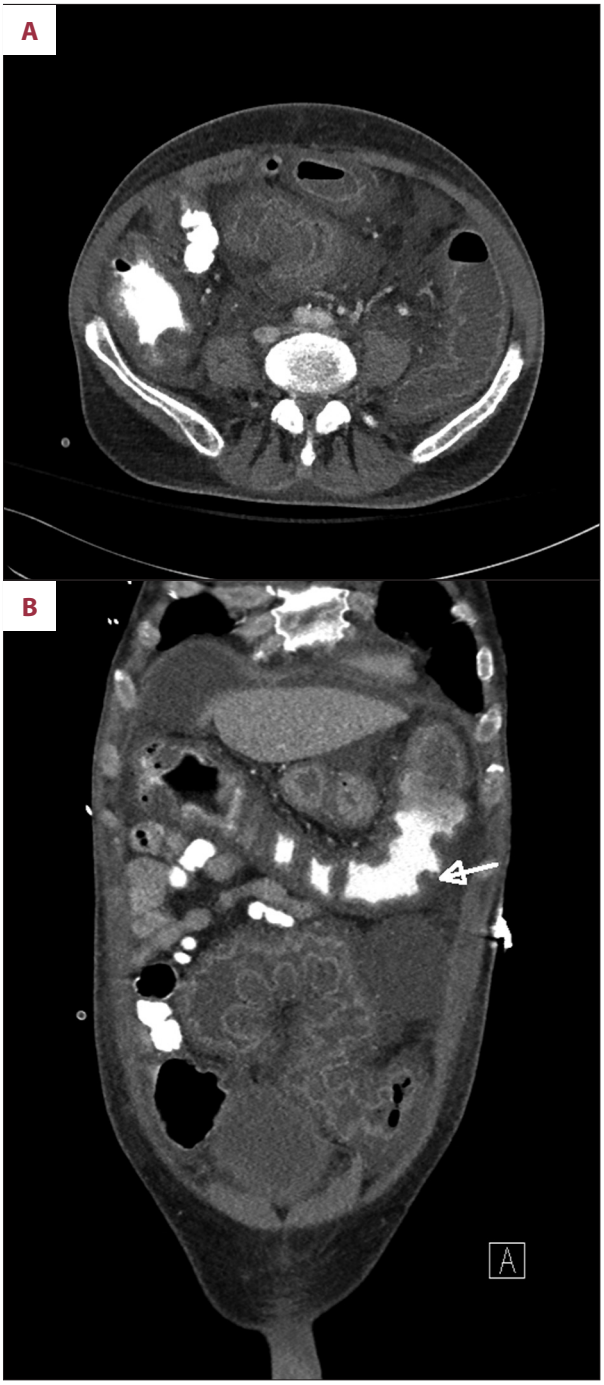

Figure 1. Axial (**A**) CT and coronal reformat images (**B**) show diffuse thickening of the colonic wall with some segments having a thumbprinted appearance (arrow).

recurrence after initial successful treatment with Vancomycin or metronidazole are around 20–30%, usually within the first 2 months. Fidaxomicin, a macrolide antibiotic has shown to be significantly effective in treating *C. diff* infection compared to vancomycin, not only because of its bactericidal effect but also from its prolonged post antibiotic effects against *C. difficile*, as well as by preserving the colonic flora [2]. In one recent report from New England Journal of Medicine, fidaxomicin and oral vancomycin have shown similar effectiveness with respect to the clinical resolution of acute diarrheal disease due to *C. difficile* [2]. The bacteriological response in our patient could be the effect of any of the medications aimed at treating *C. difficile*. There is currently no commonly agreed protocol for treatment of *C. difficile* infection as every case is different and different management plans can lead to complete recovery [4]. Given the higher incidence of severe case and increasing morbidity and mortality, use of Vancomycin as a first line drug is justified [5]. As CMV and *C. difficile* colitis have the overlapping symptomatology, the identification of individual pathogen may be delayed and hence, the treatment. Cases of CMV, *C. diff* co-infection with enterocolitis have rarely been reported in literature and most reported cases are among transplant patients who are on immunosuppressants [6].

In our case, laboratory data has revealed a successful treatment of *C. difficile* prior to the initiation of ganciclovir as evidenced by negative *C. difficile* by PCR. Although histopathological diagnosis of CMV has a high specificity, endoscopic procedure was deferred in our patient for fear of complications. Instead we obtained whole blood CMV PCR which has a high sensitivity than plasma. As a noninvasive method, we also did stool CMV PCR, which has even higher sensitivity than blood and tissue PCR. As per data available, sensitivity and specificity of CMV PCR for CMV enterocolitis is 91% and 92.1% respectively with a positive predictive value of 94.5% and negative predictive value of 87.4% [7]. CMV infection in patients with *C. difficile* colitis is either due to a coexistent infection or secondary to disruption of the colonic mucosa following the previous infection and a relative immunosuppressed state from preceding *C. difficile* infection [8]. Although most reported cases of C diff CMV co infection occur in severely immunosuppressed post-transplant patients, our case report highlights the importance of maintaining high level of clinical suspicion in other patient populations including malnourished and cancer patients. There are also very limited reports of concomitant *Clostridium difficile* and CMV coinfection and colitis in immunocompetent patients presenting with a confusing clinical picture [9].

Conclusions

We report this case to highlight the importance of looking for all potential causes of diarrhea in patients with a weak immune system. As risk factors for *C. difficile* and CMV colitis overlap, workup for both pathogens should be included in the management plan. Though histological diagnosis has high sensitivity and specificity, treatment should not be delayed in symptomatic patients with positive CMV PCR in blood and stool, as this could result in high fatality.

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