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Case Report

CMV Colitis Mimicking Crohn's Disease in a Patient with CLL: A Case Report

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Abstract

Background: Cytomegalovirus (CMV) infections are common, especially in immunocompromised patients. These infections are usually asymptomatic but can become symptomatic in immunocompromised individuals, with colitis being the second most common presentation of end-organ disease. CMV colitis can mimic Inflammatory Bowel Disease (IBD) or cause an IBD flare, thus making the diagnosis challenging.

Case Report: We describe the case of a 69-year-old male known to have Chronic Lymphocytic Leukemia (CLL) maintained in remission on venetoclax, a BCL-2 inhibitor. The patient was recently started on mesalamine and steroids after a Crohn's Disease (CD) diagnosis three weeks before presentation. The patient presented with bloody diarrhea and abdominal pain. His workup included a colonoscopy that showed skip lesions (diffuse ulcerated lesions separated by areas of normal mucosa), a characteristic of CD. Ileal and colonic biopsies were sent for Polymerase Chain Reaction (PCR) of CMV and turned out positive. Therefore, the patient was diagnosed with CD with superimposed CMV colitis. We started the patient on ganciclovir. Three months later, a repeat colonoscopy revealed complete resolution of mucosal ulcerations, practically changing the diagnosis to an isolated CMV colitis mimicking CD.

Conclusion: An isolated CMV colitis can mimic CD, and physicians must consider this entity in their differential diagnosis. This case is additionally remarkable because CLL and the use of a BCL-2 inhibitor usually have a protective role against CMV disease, but this was not the case for our patient.

Keywords: CMV Colitis; IBD; Crohn's Disease; CD; Venetoclax; CLL; BCL-2 inhibitors; Case Report

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Introduction

CMV disease is a common infection. It is usually asymptomatic but can become symptomatic in immunocompromised hosts. It can manifest in numerous organs, with colitis being the second most common presentation of end-organ disease [1]. Several articles report patients with established IBD complicated by CMV colitis [2]. However, the literature is sparse when it comes to CMV as a primary cause of isolated colitis due to the rarity of this disease [3]. CMV colitis can mimic IBD not only in the clinical aspect but also in the endoscopic and histological findings, making the distinction between the two entities more challenging [3].

In the next section, we will present a case of a CLL patient on venetoclax, a BCL-2 inhibitor, who developed an anorectal abscess and was found to have diffuse ileocolonic ulcerations and skip lesions on colonoscopy. Mucosal samples were positive for CMV on PCR testing, so a diagnosis of severe Crohn's disease complicated by CMV infection was made. After treatment with a course of ganciclovir, we noted complete resolution of the ulcerations, an unusual finding in CD.

CMV can rarely cause isolated colitis without pre-existing IBD [3]. CMV infection can coexist with IBD, but it remains unknown if CMV reactivation can cause a disease exacerbation in a patient with established IBD or if it serves as an innocent bystander of severe IBD [4]. Only a few cases of CMV colitis mimicking IBD in immunocompromised patients have been described in the literature [5,6].

CLL patients, though immunocompromised, rarely experience CMV colitis like other immunocompromised individuals, given that the anti-CMV T-cell response in CLL patients is sufficient to prevent CMV-induced disease [7].

In this report, we will examine the relation between IBD and CMV, as well as the one between CLL and CMV, and the possible roles and implications of the drug venetoclax in such a case. To our knowledge, this is the first reported case of CMV colitis in a CLL patient.

Case Presentation

A 69-year-old Middle Eastern Caucasian man presented to our Emergency Department (ED) with bloody diarrhea and abdominal pain. The patient had a past medical history of hypertension and dyslipidemia. Two years before presentation, he was diagnosed with CLL and maintained in remission on venetoclax. His family history was unremarkable. He had no previous infection-related hospital admissions since his diagnosis with CLL. Three weeks before presentation to our ED, he was diagnosed with CD in another facility based on the findings of an ulcerated ileocolitis on colonoscopy and an anal abscess which was surgically treated at that point. The patient was started on oral mesalamine with a total dose of 4 g/day, and oral prednisone with a dose of 40 mg/day.

On admission, his vital signs were within normal range. On physical examination, he had dry oral mucosa, poor skin turgor, diffuse abdominal tenderness, with fresh blood seen on rectal exam. The laboratory tests on admission showed a hemoglobin Hb of 9.9 g/dL (Normal Range [NR] = 13.5 to 17.5 grams per deciliter), Mean Corpuscular Volume MCV of 80 fL (NR=80 – 94 femtoliter), White Blood Count WBC of 8.64 x 10^9/L (NR= 4.5 to 11.0 × 10^9 per liter), C-Reactive Protein CRP of 24.4 mg/L (NR < 10 milligrams per liter), albumin of 24 g/L (NR= 34 to 54 g/L), and minor electrolytes disturbances: mild hyponatremia, hypokalemia, and hypomagnesemia. Stool analysis, stool culture, and *Clostridium difficile* toxins test were performed and came back negative. The patient was started on intravenous (IV) hydration with isotonic saline. Empiric antibiotics were started: ceftriaxone 2 g IV once daily and metronidazole 500 mg IV three times daily for the management of suspected infectious bloody diarrhea in an

immunocompromised host. Two days later, the patient developed severe rectorrhagia that resulted in a significant drop of hemoglobin (reaching 6.63 mg/dL), requiring transfusion of 2 units of packed red blood cells and prompting an urgent colonoscopy. The results of the colonoscopy showed diffuse ulcerated lesions separated by areas of normal mucosa (skip lesions) across the colon and terminal ileum with sparing of the splenic and hepatic flexures (Figure 1).

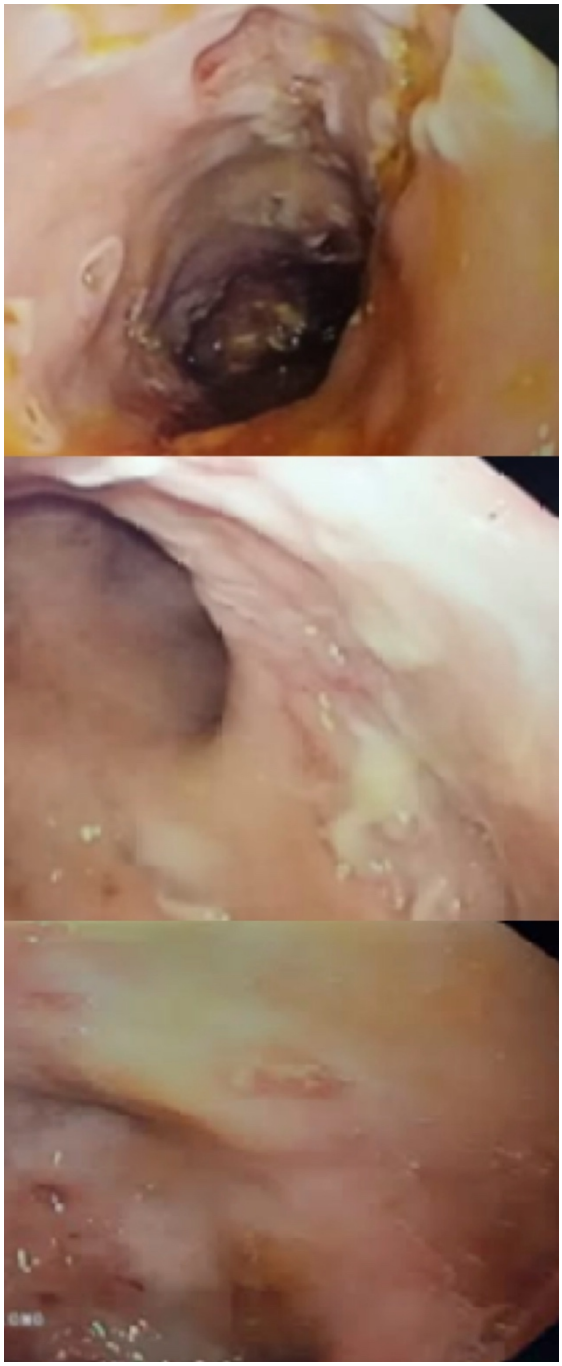

Figure 1: *Colonic ulcerations seen on the first colonoscopy.*

Histological examination of colonic and ileal biopsies showed fragments containing mixed inflammatory infiltrates with few micro-abscesses and no granulomas. A mucosal sample tested positive in qualitative PCR of CMV. Therefore, we diagnosed the patient with severe acute colitis and ileitis compatible with CD, along with superimposed CMV colitis. The patient was then started on IV ganciclovir, 500 mg every 12 hours for five days. He was later discharged on oral valganciclovir 450 mg 2 tablets twice daily for three weeks and prednisone 20 mg daily. We also resumed venetoclax and his home medications. Prednisone was tapered and stopped after two months.

The patient presented three months later with an altered mental status. Blood cultures were positive for *Listeria monocytogenes*. A lumbar puncture and CSF studies showed elevated WBC and low glucose. CSF cultures also grew *Listeria monocytogenes*, so he was diagnosed with listeria meningitis and received a course of ampicillin. At that time, a follow-up colonoscopy was performed. There was complete resolution of the ulcerations, absence of micro-abscesses, and decreased inflammation. The complete bowel healing and disappearance of all ulcers contradict the diagnosis of CD. PCR of CMV was still positive, so oral valganciclovir 450 mg 2 tablets per os twice a day was resumed for one more month.

Discussion

CMV is a common cause of infection in adults. The estimation is that by the age of 35, 50% to 80% of the general population has had CMV infection [3]. The infection is usually asymptomatic in healthy adults and symptomatic in immunocompromised patients, especially those with defective cell-mediated immunity (Acquired Immune Deficiency Syndrome AIDS patients, transplant patients, and patients receiving chemotherapy or long-term steroid therapy) [2]. CMV disease may manifest in a variety of organs but the predilection for the colon makes CMV colitis more

common [3].

Several publications report patients with established IBD developing an acute exacerbation secondary to CMV disease, with most of these patients having ulcerative colitis (UC) and fewer having CD [2]. Patients with active UC, resistant to steroids, are at an increased risk of clinically significant CMV colitis [2].

However, it is still unknown whether CMV causes exacerbation of UC or serves as an innocent bystander of severe disease. Some studies suggest that the onset of CMV infection might act as a triggering factor for the presentation of UC [8]. The clinical significance of CMV infection in IBD is different in CD and UC, as CMV does not interfere in the clinical course of CD [4].

Many reports have looked at IBD with superimposed cytomegalovirus infection, but only few have looked at cytomegalovirus as a primary cause of isolated colitis due to its rarity [3].

Since 1980, 54 cases of CMV colitis in immunocompetent patients have been reported [9]. Few cases were described in the literature of CMV colitis mimicking IBD. Kim et *al.* reviewed medical records of patients diagnosed with CMV colitis between 1998 and 2009. The study identified 43 patients including individuals with AIDS, patients undergoing chemotherapy, steroid therapy, or transplantation, in addition to individuals with other comorbidities and individuals with in addition to individuals who were previously healthy or had other comorbidities [5]. Khan et *al.* described a young male with lupus nephritis on immunosuppressants who developed CMV colitis mimicking IBD [6].

The presentation of patients with IBD flares is similar to those with CMV colitis. The clinical presentation includes non-specific symptoms such as diarrhea, abdominal pain, fever, rectal bleeding, and weight loss [5]. Furthermore, the endoscopic and histological findings of CMV colitis can mimic those of IBD. On endoscopy, the findings associated with CMV colitis include nonspecific hyperemia, micro-erosions, superficial hemorrhages, and deep ulcerations (typically a well-defined punched-out appearance) associated with residual pseudo-polyps mimicking IBD. Cobblestone-like confluent ulcers may also be seen on a pale and flattened mucosa, closely mimicking CD [10]. Histologically, CMV causes an architectural distortion with shortening of the crypts and glandular branching of the colonic mucosa, cryptitis, crypt abscesses, basal lymphoplasmacytic cellular infiltrates, and focal mucin depletion with reactive epithelial atypia, which also simulates IBD [3,10]. It's worth noting that the diagnosis of tissue invasive colonic CMV currently lies on histology with immunohistochemistry or mucosal PCR [2].

When it comes to antiviral therapy, immunocompetent patients may not need to be treated. In contrast, immunosuppressed patients, elderly patients, those with multiple co-morbidities, and those with severe diseases do require treatment [2]. In patients with IBD, treatment should be reserved for patients where CMV is evaluated as the significant driver of gastrointestinal inflammation as in the case of high tissue burden or refractory IBD with histological evidence of CMV. It is important to note that treatment of CMV colitis in IBD has been associated with a higher rate of long-term remission and a lower rate of colectomy [2].

For patients with severe infections, it is recommended to give antiviral therapy for 2-3 weeks. It is recommended to initiate intravenous ganciclovir at 5 mg/Kg every 12 hours for 5-10 days and follow that with oral valganciclovir 900 mg twice daily for the remainder of the course [11, 12]. In cases of ganciclovir resistance or intolerance (e.g. myelotoxicity), it is recommended to use foscarnet (for 2–3 weeks) [13].

Immunosuppression by corticosteroid therapy should be also reconsidered in

patients with high suspicion for tissue invasive CMV disease due to the increased risk of reactivation, so depending on the clinical course, both starting antivirals and adjusting immunosuppression may be required to achieve clinical remission [2].

In CLL, patients have a relatively impaired humoral immunity (hypogammaglobinemia) and therefore are more susceptible to infections like varicella, influenza, or pneumococci but they are paradoxically less susceptible to CMV [14]. Pourgheysari et *al.* demonstrated that the accumulation of CMV-specific T cells that normally occurs in persistent CMV infection and increases with age is even more marked in patients with CLL compared with age-matched controls [15]. CLL patients rarely experience severe illnesses like CMV pneumonitis, uveitis, and, colitis like other immunocompromised hosts, their anti-CMV T-cell response has been described as sufficient to prevent CMV-induced disease [7].

Venetoclax, taken by our patient, is an FDA-approved drug for the treatment of B-CLL, it is a potent and specific inhibitor of the anti-apoptotic BCL-2 proteins. CMV can mimic pro-survival BCL-2 proteins, hijacking the intrinsic apoptotic pathway to its benefit. By preventing host cell apoptosis, CMV maintains the infrastructure needed for its replication, therefore leading to the establishment of a persistent infection.

Anti-apoptotic BCL-2 proteins represent cellular targets for novel antivirals, and BCL-2 inhibitors display anti-viral properties [16]. We, therefore, infer a possible protective effect of venetoclax against CMV infections

The case presented here is an interesting one for two reasons. The first reason is that after the completion of the course of antiviral therapy, the colonic ulcerations disappeared completely which argues against a diagnosis of CD and rather towards a case of isolated CMV colitis mimicking IBD. The second reason is that this patient developed CMV colitis despite his medical history of CLL and his use of venetoclax, which are both considered protective against CMV as evidence suggests.

Conclusion

CMV colitis is a rare disease that can mimic IBD. Physicians often consider CMV colitis a differential diagnosis of IBD, especially in patients not responding to standard IBD treatment. Considering this differential diagnosis is necessary because the mainstay therapy for IBD is immunosuppression, which can be detrimental in the case of a CMV infection. Since CLL and BCL-2 inhibitors are considered protective factors against CMV, we concur that the diagnosis of CMV colitis in a CLL patient on venetoclax indicates that additional research in this field may be needed to further understand the immunopathogenesis of CMV infections.

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