Case Report
A case report of cytomegalovirus-induced colitis with colonic perforation

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Abstract: Cytomegalovirus (CMV)-induced colitis is a severe inflammatory reaction of the colon as a result of CMV infection. It typically presents in immunocompromised patients as a reactivated latent infection. Complications include toxic megacolon, necrotizing colitis, peritonitis, and sepsis. Colonic perforation may also result from the inflammation and ischemic injury, but it is exceedingly rare. We present a case of a patient with stage IV urothelial carcinoma who developed perforation of the sigmoid colon secondary to CMV infection. She had an unremarkable sigmoidoscopy evaluation four days prior to her presentation. The patient died two weeks after the colonic perforation in the hospital from sepsis secondary to the colonic perforation.

Keywords: Cytomegalovirus, colitis, perforation

Introduction

Cytomegalovirus (CMV) is a double-stranded DNA virus and a member of the Herpesviridae family. Viral transmission can occur via saliva, respiratory droplets, urine, blood transfusion, and sexual contact [1-6]. Although most people are exposed to the virus at some point in their lifetime, it usually produces minimal symptoms in immunocompetent people. On the other hand, more serious and aggressive CMV infections occur when the virus is reactivated after previous latent infection, most often in immunocompromised individuals.

CMV colitis is a highly serious inflammatory condition of the colon. Patients can present with fever, abdominal pain, nausea, vomiting, and bloody diarrhea. Complications include toxic megacolon, necrotizing colitis, peritonitis, and sepsis. Colonic perforation may also result from the inflammation and ischemic injury, but it is exceedingly rare. In the present report, we discuss a patient with a history of urothelial cancer who developed bowel perforation from CMV colitis with a previously unremarkable sigmoidoscopy evaluation.

Case presentation

An 80-year old female with a past medical history of stage IV urothelial carcinoma (recently treated with nivolumab and ipilimmab) and type II diabetes presented to the Emergency Room with sudden onset of abdominal pain and hematochezia. She was taking 30 mg of methylprednisolone twice daily. She had undergone sigmoidoscopy four days prior to the abdominal pain with no significant pathological findings in her colonic biopsies. Her physical examination was remarkable for lower quadrant abdominal pain without signs of guarding or rebound. Bowel sounds were normoactive and mild abdominal distension was noted. Initial laboratory tests revealed mild leukopenia (white blood cell count of $3.3 \times 10^3/\mu L$ [normal range, 3.5-12.3 $\times$ 10^3]), anemia (hemoglobin, 9.6 g/dl [normal range, 12.0-16.0]), hyponatremia (sodium, 128 mEq/L [normal range, 135-147 mEq/L]), and hyperglycemia (glucose, 244 mg/dL [normal, 70-110 mg/dL]). Serology studies were positive for CMV IgM and IgG antibodies and negative for HIV, Hepatitis B, and Hepatitis C infection. Imaging studies from the Emergency Room showed a large volume of intraperitoneal
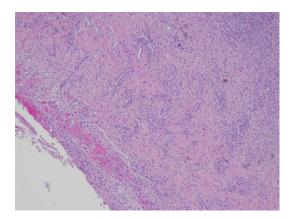
Figure 1. Colonic tissue with transmural inflammation, ulcerated mucosa, stromal inflammation, and granulation tissue is shown (hematoxylin-eosin, original magnification X4).
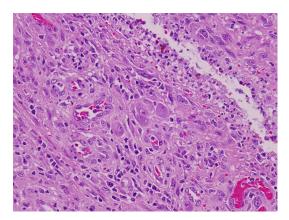

Figure 2. Colonic stromal granulation tissue is shown with diffuse lymphoplasmacytic inflammation and scattered vessels. CMV-infected stromal cells are enlarged with prominent eosinophilic nucleoli (hematoxylin-eosin, original magnifications X20).
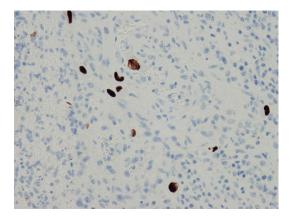

Figure 3. Immunohistochemical staining for CMV demonstrates strong nuclear positivity within infected stromal cells (original magnifications X20).

air and fluid with stranding around the sigmoid colon.

The patient was taken to the Operating Room for a sigmoid colectomy. Gross findings of the specimen revealed a transmural defect extending through the serosal surface with gray-brown exudate, consistent with perforation. Histologic examination revealed a remarkable transmural perforated area showing acute colitis with ulceration, granulation tissue, and acute serositis (**Figure 1**). Large viral inclusions with prominent eosinophilic nucleoli were seen at the site of perforation within the lamina propria and stromal and endothelial cells (**Figure 2**). These viral inclusions were positive for CMV immunostain (**Figure 3**). No malignant cells were identified in any of the examined sections to suggest urothelial carcinoma invasion.

The serological and histological findings were consistent with CMV colitis with perforation of the sigmoid colon. She was diagnosed with CMV pneumonitis 3 months prior to her current presentation; however, no other organs besides the GI tract were infected with CMV on the current admission. Gancyclovir was initiated, however the patient died two weeks later in the hospital from sepsis secondary to the bowel perforation.

Discussion

Perforated CMV colitis without an obvious local cause of perforation is exceedingly rare. The case is unique in that the patient had an unremarkable sigmoidoscopy exam four days prior to her presentation to the ER. Furthermore, the CMV inclusions present at the perforation site suggests that the viral infection may have played a primary role in the perforation.

CMV infects between 60-70% of adults in industrialized countries and almost 100% in developing countries [7]. It typically remains latent within the body after infection. Reactivation of infection typically manifests as CMV infection of the central nervous system, GI tract, and lungs. Populations at risk include neonates and the immunocompromised, especially in patients with specific histories of organ transplantation, cancer, HIV, and hemodialysis. Advanced age is also a risk factor for CMV infection due to decreased CD8+ T cells that

are critical for bowel integrity and protection [8].

Presenting signs of CMV colitis include fever, malaise and abdominal pain [9]. Watery diarrhea, tenesmus, and hematochezia can also occur [10]. Extensive mucosal ulceration, hemorrhage, and perforation can place patients at risk for life-threatening complications. Histologically, the infected endothelial and stromal cells appear enlarged with eosinophilic intranuclear and basophilic cytoplasmic inclusions. Tissue necrosis, vascular endothelial cell damage, and mucosal inflammation and hemorrhage are typically in the background. Once the diagnosis is confirmed with serological studies and/or histopathological examination, antiviral therapy (ganciclovir) is administered to mitigate the infection and prevent complications. Despite antiviral agents often being combined with colonic resection, the mortality rate remains high.

A study by Goodman et al. [11] identified 13 cases of colonic perforation in immunologically compromised patients. Causative/contributing factors were identified in 11 of the 13, including tumor, diverticulitis, arteritis, and pancreatic pseudocyst. CMV inclusions were present at the perforation site in the remaining 2 cases where no certain cause of perforation was found, suggesting that the viral infection played a role in the events leading to the perforation. Similar to our case, both of the patients in the study were receiving treatment with corticosteroids at the time of the perforation. The CMV inclusions were present in the tissue surrounding the perforation as in our case.

Kram et al. [12] reported a case of perforation of the transverse colon secondary to CMV in a 28 year old male with AIDS. Two weeks prior to his admission, the patient had positive blood cultures for Campylobacter intestinalis. Examination of the segment of resected transverse colon revealed cells with cytomegalic inclusions in the floor of an ulcer and granulation tissue consistent with CMV infection. The patient eventually died of overwhelming sepsis 13 days later. A similar case by DeRiso et al. [13] reported multiple jejunal perforations from CMV in a HIV-positive male. CMV inclusion bodies were present in all layers of the bowel, but no other pathogenic organism was identified.

Our patient differs from the previously reported cases in two aspects: 1) having no history of HIV/AIDS or previous bacterial infection of the intestinal tract that would suggest a possible synergistic cause for colonic perforation, 2) lack of any pathologic findings in a sigmoidoscopy evaluation to suggest any sort of mucosal injury/infection. Our case also poses the question of whether CMV was the primary cause of the colonic perforation or instead a secondary or opportunistic cause. Viral inclusions have been reported in pseudomembranous colitis [14-18], ulcerative colitis with toxic megacolon [19], and in solitary ulcers [20-23], suggesting that CMV is an opportunistic infection in cases with inflammation and ulceration. Rare cases of CMV infections in presence of solitary ulcers without a recognized cause of ulceration have also been reported [20-23], suggesting that the virus may indeed cause the perforation rather than an incidental finding.

There are multiple mimickers of CMV colitis that must always be considered as a differential diagnosis prior to diagnosing the patient with CMV. Herpetic colitis, or infection with Herpex Simplex Virus (HSV), has a similar morphology to CMV. HSV, unlike CMV, displays nuclear molding, glassy nuclear inclusions, and multinucleation. Common bacterial causes of colitis include Shigella, E Coli, Salmonella and Campylobacter. These can be distinguished from CMV colitis by the predominant neutrophil infiltration of the lamina propria. Pseudomembranous colitis also shows a predominance of neutrophils in addition to pseudomembranes covering the colonic epithelial surface. Bacterial and pseudomembranous colitis must be ultimately diagnosed by stool culture.

CMV infection can also reactivate in patients Inflammatory bowel diseases (IBD) due to active injury to the gut mucosa and also immunosuppression from steroid treatment [24, 25]. Thus, Crohn's disease and ulcerative colitis must also be considered as underlying causes of colitis when CMV changes are identified.

In our patient's case, her history of prior chemotherapy for metastatic urothelial carcinoma, daily intake of methylprednisolone, diabetes, and advanced age were all factors placing her at risk for CMV colitis. Her presenting signs and symptoms of acute abdominal pain with GI bleeding were consistent with CMV infection. It

is unclear, however, what underlying or alternative factors may have made her gut prone to CMV reactivation and perforation. She was diagnosed with CMV pneumonitis approximately 3 months prior to her presentation, however, no other organs besides the GI tract were affected with CMV at the time of her presentation. No changes of chronicity (basal cell plasmacytosis, architectural distortion) were seen on microscopic examination to suggest an underlying IBD. Furthermore, the previous normal findings during her sigmoidoscopy in addition to the unremarkable random colon biopsies from the procedure makes IBD, bacterial colitis, and pseudomembranous colitis all less plausible.

Some might argue that the colonic perforation was a result of invasive urothelial carcinoma. This is unlikely provided that no malignant cells were identified on microscopic examination of the resected sigmoid colon or on the previously submitted random colon biopsies from the sigmoidoscopy. An additional argument might be that her colon ruptured from iatrogenic perforation from the sigmoidoscopy four days prior to her presentation. Although this remains a possibility, no muscularis propria was identified in any of the random colon biopsies submitted for microscopic examination, making an iatrogenic bowel perforation less likely.

This case illustrates how quickly CMV colitis may lead to colonic perforation. It also sheds light on the pathogenesis of CMV colonic infection and suggests that an underlying insult to the gut mucosa may not be required for CMV reactivation. More studies are needed to further investigate the pathogenic mechanisms of CMV in patients without a history of IBD, HIV, or underlying infectious colitis.

Conclusion

In conclusion, this case presents a unique finding of bowel perforation secondary to CMV colitis. It highlights the urgency of detecting the early symptoms and signs (abdominal pain, GI bleeding, and diarrhea) of CMV colitis in the elderly and immunocompromised. Furthermore, it reminds medical professionals that no one patient is the same. Likewise, every patient's unique needs should be considered with regards to immunosuppressant regimens and antiviral prophylaxis.

Disclosure of conflict of interest

The authors whose names are listed immediately below certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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References

[1] Ko JH, Peck KR, Lee WJ, Lee JY, Cho SY, Ha YE, Kang CI, Chung DR, Kim YH, Lee NY, Kim KM, Song JH. Clinical presentation and risk factors for cytomegalovirus colitis in immunocompetent adult patients. Clin Infect Dis 2015; 60: e20.

[2] Jordan MC, Rousseau WE, Noble GR, Steward JA, Chin TD. Association of cervical cytomegaloviruses with venereal disease. N Engl J Med 1973; 288: 932.

[3] Pass RF, Little EA, Stagno S, Britt WJ, Alford CA. Young children as a probable source of maternal and congenital cytomegalovirus infection. N Engl J Med 1987; 316: 1366.

[4] Adler SP. Molecular epidemiology of cytomegalovirus: viral transmission among children attending a day care center, their parents, and caretakers. J Pediatr 1988; 112: 366.

[5] Tolpin MD, Stewart JA, Warren D, Mojica BA, Collins MA, Doveikis SA, Cabradilla C Jr, Schauf V, Raju TN, Nelson K. Transfusion transmission of cytomegalovirus confirmed by restriction endonuclease analysis. J Pediatr 1985; 107: 953.

[6] Blackman JA, Murph JR, Bale JF Jr . Risk of cytomegalovirus infection among educators and health care personnel serving disabled children. Pediatr Infect Dis J 1987; 6: 725.

[7] Fülöp T, Larbi A, Pawelec G. Human T cell aging and the impact of persistent viral infections. Front Immunol 2013; 4: 1-9.

[8] Hadrup SR, Strindhall J, Køllgaard T, Seremet T, Johansson B, Pawelec G, thor Straten P, Wikby A. Longitudinal studies of clonally expanded CD8 T cells reveal a repertoire shrinkage predicting mortality and an increased number of dysfunctional cytomegalovirus-specific T cells in the very elderly. J Immunol 2006; 176: 2645-2653.

[9] Galiatsatos P, Shrier I, Lamoureux E, Szilagyi A. Meta-analysis of outcome of cytomegalovirus

colitis in immunocompetent hosts. Dig Dis Sci 2005; 50: 609-616.

[10] Vanegas F, Montalvo RD, Alvarez OA, Donelson SS, Lee M. Massive upper gastrointestinal hemorrhage due to cytomegalovirus infection in two patients with acquired immunodeficiency syndrome. South Med J 2000; 93: 235.

[11] Goodman ZD, Boitnott JK, Yardley JH. Perforation of the colon associated with cytomegalovirus infection. Dig Dis Sci 1979; 24: 376-380.

[12] Kram HB, Hino ST, Cohen RE, DeSantis SA, Shoemaker WC. Spontaneous colonic perforations secondary to cytomegalovirus in a patient with acquired immune deficiency syndrome. Crit Care Med 1984; 12: 469-471.

[13] DeRiso AJ, Kemeny MM, Torres RA. Multiple jejunal perforations secondary to cytomegalovirus in a patient with acquired immune deficiency syndrome. Case report and review. Dig Dis Sci 1989; 34: 623-9.

[14] Misra MK, Kinkus GS, Birtch AG, Wilson RE. Major colonic disease complicating renal transplantation. Surgery 1973; 73: 942-948.

[15] Keren DF, Milligan FD, Strandberg JD, Yardley JH. Intercurrent cytomegalovirus colitis in a patient with ulcerative colitis. Johns Hopkins Med J 1975; 136: 178-182.

[16] Wong T, Warner NE. Cytomegalic inclusion disease in adults. Arch Pathol 1962; 74: 403-422.

[17] Levine RS, Warner NE, Johnson CF. Cytomegalic inclusion disease in the gastrointestinal tract of adults. Ann Surg 1964; 159: 37-48.

[18] Nakoneczna I, Kay S. Fatal disseminated cytomegalic inclusion disease in an adult presenting with a lesion of the gastrointestinal tract. Am J Clin Pathol 1967; 47: 124-128.

[19] Cooper HS, Raffensperger EC, Jonas L, Fitts WT. Cytomegalovirus inclusions in patients with ulcerative colitis and toxic dilatation requiring colonic resection. Gastroenterology 1977; 72: 1253-1256.

[20] Hensen D. Cytomegalovirus inclusion bodies in the gastrointestinal tract. Arch Pathol 1972; 93: 477-482.

[21] Wolfe BM, Cherry JD. Hemorrhage from cecal ulcers of cytomegalovirus infection. Ann Surg 1973; 177: 490-494.

[22] Goodman MD, Porter DD. Cytomegalovirus vasculitis with fatal colonic hemorrhage. Arch Pathol 1973; 96: 281-284.

[23] Clavadetscher P, Sulser H, Linder E, Deyhle P. Ztomegalie-ulkus im coecum nach nierentransplantation. Dtsch Med Wochenschr 1974; 99: 1970-1972.

[24] Eyre-Brook IA, Dundas S. Incidence and clinical significance of colonic cytomegalovirus infection in idiopathic inflammatory bowel disease requiring colectomy. Gut 1986; 27: 1419-1425.

[25] Wakefield AJ, Fox JD, Sawyerr AM, Taylor JE, Sweenie CH, Smith M, Emery VC, Hudson M, Tedder RS, Pounder RE. Detection of herpesvirus DNA in the large intestine of patients with ulcerative colitis and Crohn's disease using the nested polymerase chain reaction. J Med Virol 1992; 38: 183-190.