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Brief Communication

Cytomegalovirus proctitis in non-human immunodeficiency virus infected patients: A case report and literature review

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Abstract Cytomegalovirus (CMV) infection is associated with significant morbidity and mortality in both immunocompetent and immunocompromised patients. CMV is a ubiquitous Herpesviridae virus with a wide spectrum of pathologies in humans. Immunocompetent patients generally develop a benign, self-limited mononucleosis-like syndrome, whereas gastrointestinal tissue-invasive disease is more frequently seen in immunocompromised. The clinical manifestations of CMV colitis or proctitis are demarcated by bloody diarrhea, ulcerations, ulcero-infiltrative changes, and pseudomembranous formation on colonoscopy. Gastrointestinal CMV infections complicated with deep rectal ulcer and fistula formation are rare in patients with systemic lupus erythematosus. Ganciclovir is also the gold standard therapy for CMV colitis or proctitis.

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Introduction

Cytomegalovirus (CMV) is a member of the herpes virus family. CMV infection is an opportunistic infection in both immunocompetent and immunocompromised patients, and it could lead to significant morbidity and mortality.[1,2] We present a case of CMV proctitis in a systemic lupus erythematosus (SLE) patient who complicated with a deep ulcerative fistula. He was successfully treated with a complete course of ganciclovir.[1—6]

Case presentation

This 71-year-old man had past histories of SLE complicated with bilateral optic nerve atrophy, two cyclophosphamide therapies on April 18 and May 16, 2018, and a disease-modifying antirheumatic drug (DMARD) therapy with hydroxychloroquine for over two years; he also had hepatitis C carrier status after complete Harvoni (anti-hepatitis C virus) treatment. He also had benign prostate hypertrophy, dyslipidemia, and right lateral medullary infarction.

He initially presented with fever, chills, intermittent urine retention, and hematuria for one week, so he visited our emergency department on July 13, 2020. Physical examination revealed suprapubic distention with tenderness, and right scrotal tenderness with mild swelling. Laboratory data showed stage 2 chronic kidney disease, borderline leukocytosis with neutrophil predominance, and elevated CRP (8.0 mg/dL). The ANA (anti-nuclear antibody) titer showed 1: 40. Urinalysis showed hematuria. Sonography showed chronic parenchymal liver disease and bilateral renal stones. Under the impression of acute urinary retention complicating urinary tract infection and epididymitis, the patient was admitted for antibiotic treatment and management.

However, hematochezia was noted on the 8th day of admission; thus, a colorectal surgeon was consulted. Digital examination revealed dark red bloody stool with malodor. A firm deformity over the posterior rectal wall was noted; hence, malignancy could not be ruled out. Tumor markers, including CEA, CA-199, and SCC, were all within the normal limits. Colonoscopy revealed a deep ulcer, 4 × 3 cm in size, in the posterior rectal wall (Fig. 1a). A biopsy was performed. Microscopic findings revealed a colorectal ulcer with fibrinoid necrotic debris, granulation tissue formation, and acute and chronic inflammatory cell infiltration. Some infected cells showed intranuclear viral inclusions. Immunohistochemical (IHC) staining confirmed CMV infections (Fig. 2b). CMV proctitis was diagnosed clinically.

The patient also underwent serological tests for CMV IgG and IgM. The CMV IgG level was >500, while IgM was negative. Human immunodeficiency virus (HIV) antigen (Ag)-antibody (Ab) combination assay was negative. The CD4 and CD8 absolute counts were both within the normal limits. Stool routine examination showed positive occult blood (3+). Stool and blood culture both showed no growth for over five days, and cryptococcal Ag and *Clostridium difficile* toxin were both negative. Pelvic MRI revealed concentric wall thickening of the rectum and fat stranding of the perirectal fascia with outpouching and possible fistula formation in the right posterior aspect (Fig. 3a—d). The finding was compatible with complicated CMV proctitis.

The patient received intravenous ganciclovir 300 mg Q12H for 14 days. We found no hematochezia or bloody stool after the complete course of therapy. The patient recovered without sequelae 14 days after ganciclovir treatment. Follow-up sigmoid fibroscopy revealed that the lesion recovered with newly grown mucosal tissue (Fig. 2b).

Literature review of CMV proctitis

We searched for literature in PubMed from 1980 to 2020 that was written in English, with accessible full article, and with the term "immunocompetent AND (cytomegalovirus OR CMV) AND (proctitis OR proctal OR rectal OR rectum)".[1—3] Relevant articles were also reviewed for potential cases.[4—10] A total of 20 (including the present case) cases of CMV proctitis in immunocompetent patients were identified from 12 published articles.[10—21] Patient characteristics, comorbidities, clinical manifestations, endoscopic findings, treatment, outcomes, and reassessment methods were analyzed (Table 1).[5—14]

In a review of these 20 cases, the mean age was 70.5 years (range, 40—92 years old); 14 cases were female (70.0%); 15 had comorbidities (75.0%); eight had DM

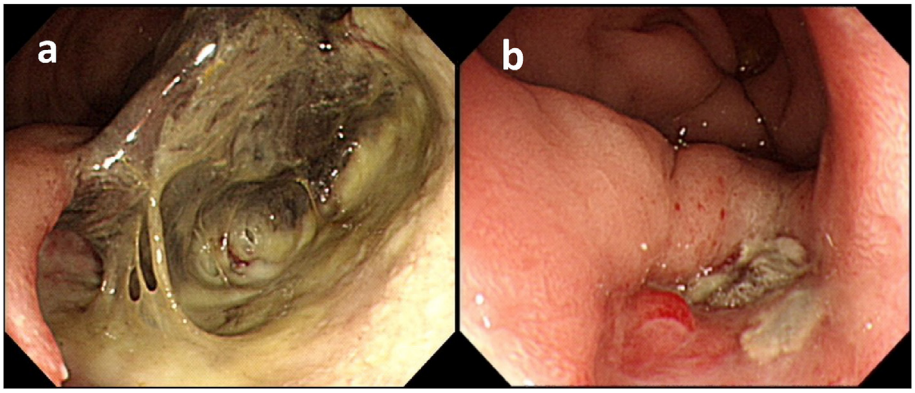

Figure 1. Colonoscopy before and after antiviral therapy. **a,** A deep ulcer in the posterior rectal wall with marginal granulation. **b,** After 14 days of antiviral treatment, the ulcer was healing with newly grown mucosal tissue.

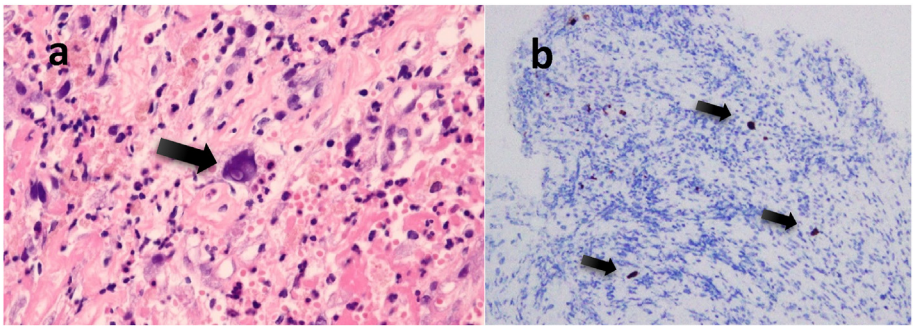

Figure 2. **a**, Microscopic examination of rectal biopsy (×400, H&E stain). The large, infected cell showed intranuclear viral inclusion with perinuclear halo. **b,** Immunohistochemical staining (×100) with the monoclonal mouse antibody (Dako) for cytomegalovirus (arrow).

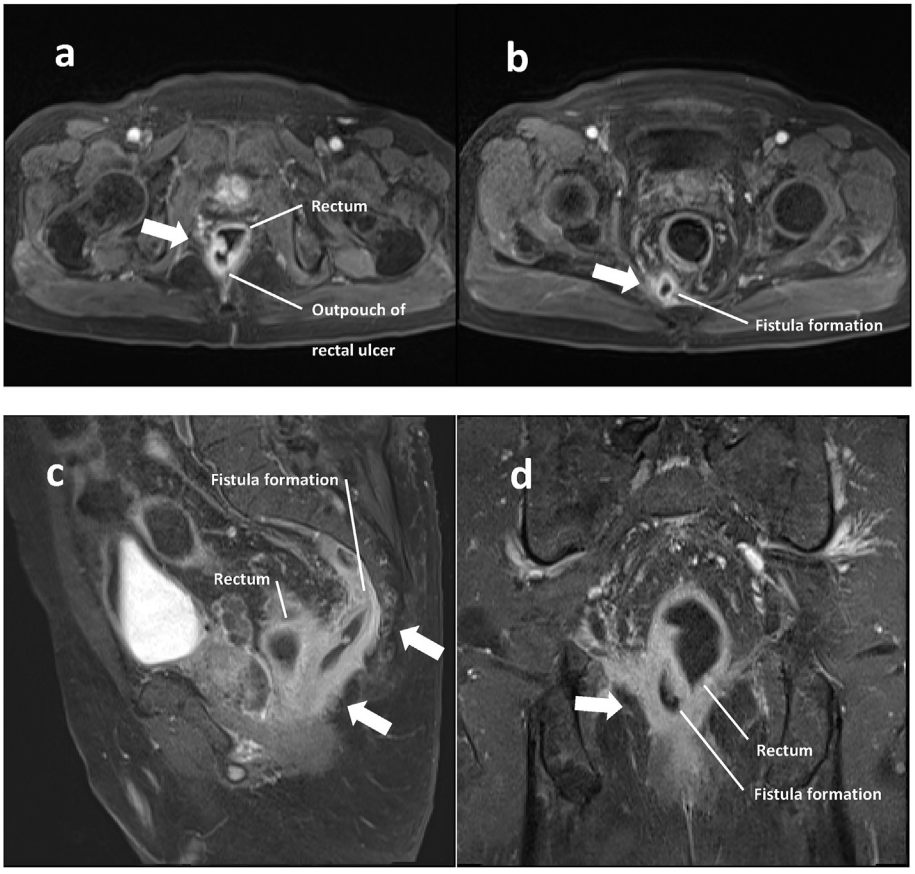

Figure 3. Pelvic MRI with contrast enhancement (T1-weighted fast spin echo [FSE] images). **a b,** Transverse view: a deep ulcer with fistula formation at right posterior rectal wall. **c,** Sagittal view: the estimated depth of the ulcer was about 6 cm with fat stranding of the perirectal fascia. **d,** Coronal view: an outpouching ulcer with fistula formation (arrows).

(40.0%); and only our current case had autoimmune disease (5.0%). Thirteen cases initially presented with bloody diarrhea or hematochezia (65.0%), and four had abdominal pain (20.0%). Endoscopic examination was performed in all cases.[13–15,25–28] CMV proctitis in immunocompetent hosts presented with various severities of rectal ulcers (85.0%), polypoidal masses (30.0%), and rectal fistulas or sinus tracts (10.0%). Two cases were endoscopically diagnosed with rectal carcinoma; however, both had CMV proctitis with no malignancy found.[15–20]

Among these 20 cases, three patients received surgical intervention (15.0%). One patient recovered smoothly after colostomy and antiviral treatment, but the treatment was not favorable for other two. One patient, who underwent sigmoid colic and rectal resection for ischemia and multiple perforations, ended up with end colostomy and three weeks of antiviral treatment.[13–22] In addition, under the condition of deterioration, sepsis, and multiorgan failure, the patient received emergent proctectomy and colostomy for massive rectal bleeding with acute anemia and

Table 1 Clinical characteristics, comorbidities, treatment, outcomes, and reassessment of 20 cases of CMV proctitis in immunocompetent patients.

Case, Ref., Published year	Age /Gender	Comorbidities	Presenting Symptoms	Preceding diagnosis	Endoscopic findings	Treatment (duration, days)	Outcome	Reassessment
1,[5] 2020	40/F	N/A	Hematochezia	CMV-related neuromyelitis optica	Rectal large ulcer-like lesion with blood clot	Ganciclovir (28)	Improved	Colonoscopy
2,[6] 2019	76/F	AAA, ESRD under hemodialysis	Bloody stool	NSTEMI	Rectal clean-base healing ulcer	Ganciclovir	Improved	N/A
3,[7] 2017	88/M	DM, HTN	Abdominal pain, nausea, diarrhea	Infectious colitis	Rectal multiple large ulcers	Resection for ischemic and perforated sigmoid colon and rectum, Ganciclovir (21)	End colostomy Loss follow up	N/A (refused)
4,[8] 2017	79/F	DM, IHD, MDD	Abdominal pain, diarrhea, tenderness	Metabolic encephalopathy, delirium	Rectal ulcer	Valganciclovir	Improved	Colonoscopy
5,[9] 2016	88/F	Paroxysmal AF, HTN, CKD, anemia	Abdominal pain, diarrhea	Rectovaginal fistula	Anorectal junction pseudopolypoid ulcer	Unknown	Expired (aspiration pneumonia)	N/A
6,[10] 2015	42/M	N/A	Diarrhea, weight loss	Rectal carcinoma	Fungating, ulcerated, obstructive mass	Ganciclovir (21)	Improved (no malignancy)	Colonoscopy Barium enema
7,[11] 2015	76/F	N/A	Abdominal pain, constipation	Rectal carcinoma	Anorectal junction polypoidal mass	Ganciclovir (14)	Improved (no malignancy)	Colonoscopy
8,[12] 2014	79/M	Stoke, HTN, DM, CKD	Bloody diarrhea	NSTEMI	Rectal ulcer	Supportive	Improved	N/A
9,[13] 2007	71/M	DM, 2nd degree heart block	Hematochezia	Esophageal adenocarcinoma, esophagectomy	Multiple rectal ulcers	Emergent proctectomy and colostomy	Expired (Massive rectal bleeding)	N/A
10,[14] 1999	57/F	DM	Diarrhea, difficult defecating	Pneumonia, K.P bacteremia	Multiple rectal ulcer with fistula and sinus tracts	Ganciclovir (21)	Improved	Sigmoidoscopy Barium enema
11,[6] 1999	83/F	DM, stroke	Bloody diarrhea	N/A	Rectal ulcer	Supportive	Improved	Proctoscopy Barium enema
12,[6] 1999	71/F	Glaucoma	Bloody diarrhea	Shigella dysentery	Rectal ulcer	Supportive	Improved	N/A (refused)
13,[6] 1999	59/F	HTN, CKD	Bloody diarrhea	AMI with cardiogenic shock	Rectal erosions	Supportive	Expired (heart failure and renal failure)	Colonoscopy
14,[6] 1999	63/M	IHD, CKD	Diarrhea and fever	AMI, stroke	Rectal erythema	Supportive	Expired (pneumonia)	N/A
15,[6] 1999	69/F	DM	Hematochezia	HHS diabetic coma, pneumonia and	Rectal ulcer	Supportive	Expired pyleonephritis)	Proctoscopy

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Table 1 (*continued*)

Case, Ref., Published year	Age /Gender	Comorbidities	Presenting Symptoms	Preceding diagnosis	Endoscopic findings	Treatment (duration, days)	Outcome	Reassessment
				cystitis				
16,[6] 1999	92/F	Meningioma	Bloody diarrhea	Cholangitis	Rectal ulcer	Ganciclovir	Improved	Proctoscopy
17,[6] 1999	67/F	HTN	Hematochezia	Cystitis	Rectal polyp	Ganciclovir, Colostomy	Improved	Colonoscopy
18,[6] 1999	74/F	DM, osteoporosis Parkinsonism	Bloody diarrhea	N/A	Sessile growth at rectum	Ganciclovir	Expired (septic shock)	Proctoscopy
19,[15] 1988	65/M	N/A	Hematochezia	Traffic accident	Rectal polypoid mass and punch-out ulcers	Sulfasalazine	Improved	Colonoscopy
20, current case	71/M	SLE, HCV carrier, BPH, old stoke	Hematochezia	Urinary tract infection with epididymitis	Deep rectal ulcer with fistula formation	Ganciclovir (17)	Improved	Sigmoidoscopy

Abbreviations: AAA abdominal aortic aneurysm, AMI acute myocardial infarction, AF atrial fibrillation, BPH benign prostate hypertrophy, CKD chronic kidney disease, DM diabetes mellitus, ESRD end stage renal disease, F female, HCV hepatitis C virus, HHS hyperosmolar hyperglycemic state, IHD ischemic heart disease, K.P *Klebsiella pneumoniae*, M male, MDD major depressive disorder, N/A not available, NSTEMI non-ST elevation acute coronary syndrome, SLE systemic lupus erythematosus.

hemoglobin dropped to 5.1 g/dL. The patient expired due to uncontrollable generalized peritoneal oozing, despite re-exploration and administration of all possible hemostatic methods. Eventually, CMV proctitis was diagnosed by autopsy histology.[22–25] On the other hand, nine patients received antiviral therapy (45.0%) and six received supportive treatment (30.0%). Only one patient expired in the antiviral therapy group; three of six patients in the supportive treatment group expired due to other comorbidities.[18–25] In addition, 13 patients had follow-up for reassessment (65.0%), and all of them underwent follow-up endoscopic examination, including proctoscopy, sigmoidoscopy, or colonoscopy.[5,6,12–22]

In a review of SLE patients with CMV infection, a case–control study concluded that CMV patients who received higher doses of glucocorticoids can develop more co-infections.[15,16] In patients with rheumatologic disease, CMV reactivation occurs, which can result in severe clinical sequelae, and is difficult to distinguish from a flare of the underlying disease. CMV should be considered during the evaluation of a febrile illness in this complex patient population.[15–20]

CMV infections in gastrointestinal tract

In general population, GI CMV disease almost always occurs in patients with relative immunosuppression due to critical illness or comorbidities, such as diabetes mellitus, prolonged residence in intensive care unit, autoimmune diseases, or organ failure.[17–20]

In all patients undergoing endoscopy, approximately 30% of GI CMV cases occurred in patients without overtly compromised immunity or IBD, with an overall prevalence of approximately 3 in 1000 endoscopies.[10,18,19] Among this population, the colon is the most frequently reported site of involvement, comprising up to 94% of cases, while rectal involvement is rare.[1,10,20,21]

Clinical manifestations of GI CMV infections vary and depend largely on the site of involvement. Symptoms of hematochezia, weight loss, abdominal pain, diarrhea, and hemorrhage can otherwise be present with involvement of any part of the GI tract. Endoscopic findings also range from mucosal inflammation and edema to cobble stone and severe ulceration.[1,9,22–24]

CMV is found in 10–38% of patients with active ulcerative colitis (UC) based on histology and the mucosal PCR technique.[1,25,26] CMV detection in patients with active Crohn's disease (CD) is less common due to its Th1-driven pathophysiology, resulting in high levels of IFN-γ, which inhibits CMV replication. CMV colitis is the most common manifestation of CMV disease in IBD, and given the similarity in clinical presentation with an acute IBD flare, determining the primary process clinically can be challenging.[1,27]

Patients with active UC resistant to corticosteroids or multiple lines of immunosuppressive therapy are at an increased risk of clinically significant CMV colitis.[1,27,28] Approximately one-third of patients with steroid-refractory UC have CMV colitis, significantly more than steroid-responsive or inactive diseases.[1,26,28] Multiple cohort studies demonstrated an increased rate of histologic detection and virologic burden of CMV based on tissue IHC staining and PCR examination in patients with steroid-

refractory UC, compared to those with steroid-responsive disease.[1,27,28] A high-serum CMV viral load can be suggestive of steroid refractoriness in active UC.[1,23,24]

Treatment of CMV infection in patients with IBD should be reserved for patients in whom GI CMV is a significant driver of colonic inflammation. CMV, as a pathogen in the setting of active IBD, has been demonstrated in patients in whom antiviral therapy and immunosuppression reduction have induced significant clinical improvement.[23—25] Untreated CMV infection in IBD is generally associated with an increased risk of hospitalization, colectomy, and mortality compared to IBD patients without active CMV.[20—23] Since CMV infection in patients with IBD is associated with rare IHC staining in approximately 50% of histologic specimens, most cases of CMV in GI tissues are likely reactivated due to local immune dysregulation that has no or minimal clinical consequences.[1,25,26] On the other hand, high CMV tissue burden has been shown to correlate with steroid-refractory IBD and response to antiviral therapy.[27,28] Therefore, antiviral therapy in refractory UC with histologic evidence of CMV, or in UC patients with high burden of tissue CMV should be strongly considered.

Conclusion

CMV colitis or proctitis can be seen in immunocompetent patients. Clinicians should consider it when patients present with painless hematochezia or bloody diarrhea. We call for awareness of opportunistic CMV infection in patients with comorbidities or under immunoregulatory treatment. Early diagnosis and treatment with appropriate antiviral therapy are crucial. Surgical intervention should be evaluated according to clinical presentation and examination findings.

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