

Herpes Simplex Virus Colitis in a Patient With Crohn's Disease and Hepatitis B and D Cirrhosis

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Herpes simplex virus (HSV) is recognized as a cause of gastrointestinal infection in patients with underlying immunodeficiency. The esophagus, perineum, and rectum are the most common sites of involvement, though diffuse colitis is rare. We present the case of a patient with Crohn's disease as well as hepatitis B virus (HBV) and hepatitis D virus (HDV) cirrhosis who presented with a refractory Crohn's disease flare that was found to be secondary to HSV colitis.

Case Report

A 50-year-old white man with a past medical history significant for Crohn's disease and HBV and HDV cirrhosis presented with a complaint of bloody stools. The patient was enrolled in the National Institutes of Health trial of pegylated interferon (IFN) for HDV. His Crohn's disease maintenance therapy had consisted of mesalamine with intermittent acute flares previously treated with antibiotics with resultant symptom resolution and induction of remission. IFN and mesalamine were discontinued 6 months prior to presentation due to a foot abscess, which was treated conservatively. The patient was subsequently treated for a presumed Crohn's disease flare with antibiotics 2 months prior to this presentation, and IFN was restarted at that time. The patient subsequently developed progressive weakness, weight loss, abdominal pain, and rectal bleeding. He was then admitted to an outside hospital where he was again treated for a presumed Crohn's disease flare with steroids and antibiotics prior to transfer to our facility.

On admission to our facility, the patient's vital signs were within the normal range and he was noted to be afebrile. Physical examination was negative for encephalopathy. The patient exhibited temporal wasting, and the abdominal examination was notable for distention as well as right upper quadrant tenderness to palpation. Laboratory evaluation was notable for a serum sodium level of 134 mmol/L, aspartate aminotransferase of 50 IU/L, alanine aminotransferase of 38 IU/L, alkaline phosphatase of 291 IU/L, serum albumin of 2.0 g/dL, white blood cell count of 11,000/ μ L with 91% neutrophils, hemoglobin of 11.0 g/dL, platelet count of 70,000/ μ L, and international normalized ratio of 1.5. Serum cytomegalovirus (CMV) polymerase chain reaction (PCR) testing was negative. The patient was initially placed on bowel rest and started on total parenteral nutrition. Intravenous antibiotics and steroids, as well as oral mesalamine, were continued. Stool cultures were obtained and found to be negative for routine bacterial and parasitic pathogens. An abdominal computed tomography scan demonstrated diffuse contiguous bowel-wall thickening extending from the ascending colon to the rectum. There was also a large amount of generalized ascites. No lymphadenopathy, hepatic masses, or mesenteric abnormalities were noted. The patient was referred for endoscopic evaluation. On colonoscopic examination, the colon was diffusely erythematous, friable, and ulcerated with purulent exudate visible throughout the examined colon (Figure 1). Biopsy specimens obtained from the colonic mucosa showed ulcerated mucosa with fibrinous necrosis. Herpes simplex viral inclusions, confirmed by immunofluorescent staining, were noted within the surface epithelium and ulcer bed (Figures 2–4). CMV and adenovirus immunostaining were negative. Colonic tissue viral culture was positive for HSV type 2. Steroid therapy was then discontinued, and the patient was treated with antiviral therapy for HSV with subsequent

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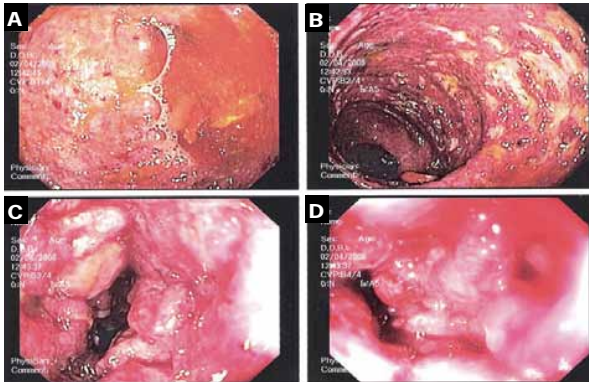


Figure 1. Endoscopic views of the colon.

rapid cessation of abdominal pain and bloody stools. However, he developed progressive hepatic decompensation and subsequently expired. The patient was not evaluated for liver transplantation in the acute setting due to the presence of infection and the rapidly progressive decline in clinical status.

Discussion

Evaluation and treatment of an acute exacerbation of Crohn's disease begins with the identification of exacerbating factors and exclusion of acute infection. Factors known to exacerbate an acute flare include cigarette smoking, nonsteroidal anti-inflammatory drug usage, and infections, including both upper respiratory and enteric infections such as *Clostridium difficile*.¹ Diarrheal relapses in patients with ulcerative colitis have also been shown to be associated with enteric infections, and timely diagnosis may lessen avoidable exposure to corticosteroids and immunosuppressants.² However, atypical etiologies should also be considered in those patients who fail to respond to therapy, particularly those who are immunosuppressed.

HSV proctitis has frequently been reported in immunocompromised patients presenting with anorectal pain, discharge, tenesmus, or hematochezia³; in contrast, diffuse colonic involvement with HSV is very rare and has been reported previously in 1 patient with Crohn's disease,⁴ but not in any patients with HBV and HDV cirrhosis. The majority of reported cases have occurred in patients who were immunosuppressed, had a defect in cellular immunity, or had a malignancy (eg, a bone marrow transplant recipient who also had intercurrent CMV, *C. difficile* infection, and graft-versus-host disease,⁵ a patient with common variable immunodeficiency syndrome presenting with HSV-1,⁶ a patient with HSV-1 who had under-

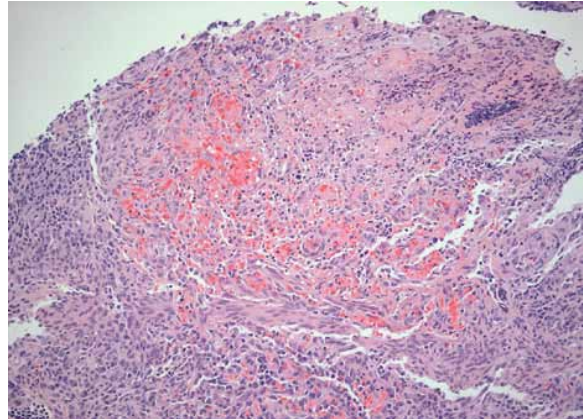


Figure 2. Granulating ulcer with necrotic exudate (hematoxylin and eosin stain).

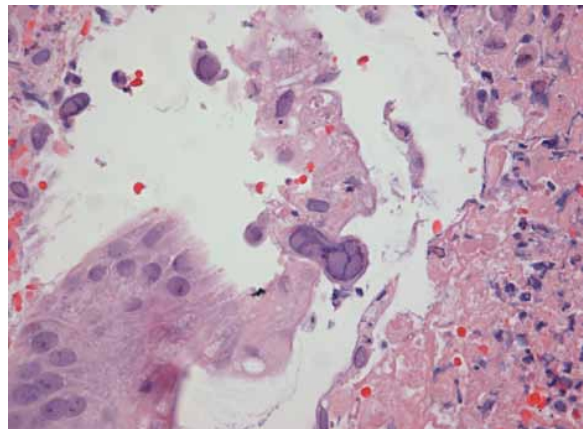


Figure 3. Cowdry type A intranuclear inclusions of herpes simplex virus forming the characteristic "eggs-in-a-basket" syncytia (hematoxylin and eosin stain).

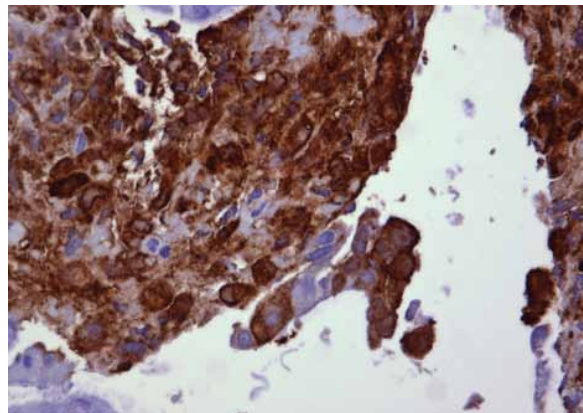


Figure 4. Infected cells display nuclear and cytoplasmic immunoreactivity for herpes simplex virus (SIGNET polyclonal Ab SIG-3435).

gone surgical treatment for adenocarcinoma of the transverse colon,⁷ and a child who had received a combined liver and small bowel transplant⁸). There has also been a case report of a neonate with congenital HSV infection with hemochezia and late sigmoid perforation.⁹

Endoscopic evaluation with biopsies was necessary in this patient to establish an etiology for his refractory flare in order to initiate appropriate treatment. With regard to pathologic evaluation for HSV, studies have been performed to determine the optimal methods for diagnosis in patients with HSV esophagitis, given its higher prevalence than HSV colitis. McBane and Gross, Jr. reported that the culture test for HSV was slightly more sensitive than microscopic examination (Cowdry type A inclusions) for the diagnosis of herpes simplex esophagitis (HSE) and that both tests should be employed in any immunosuppressed patients with esophagitis or esophageal ulcers.¹⁰ More rapid detection methods as well as microscopic investigation are necessary in practice, due to the length of time it can take for culture results to be finalized. The application of in situ hybridization or PCR assay in addition to immunohistochemical techniques with esophageal specimens may improve the diagnostic sensitivity for HSE. The immunoperoxidase method revealed diffuse positive staining in the nucleus and cytoplasm, whereas in situ hybridization revealed fibrillar positive staining in the nucleus only. Thus, the immunoperoxidase method using rabbit anti-human HSV can detect the presence of HSV protein with a greater sensitivity than that of in situ hybridization, most likely due to the greater quantity of HSV protein than HSV DNA in infected cells.¹¹

Conclusion

HSV is a known pathogen in the gastrointestinal tract, primarily in the esophagus and rectum, in patients who are immunosuppressed. This case report is not only an example of HSV colitis, which is very rare, but of a patient with both Crohn's disease and cirrhosis. This case also demonstrates the need to consider HSV in the diagnosis of refractory colitis in order to reduce the morbidity and mortality of this disease entity. This is particularly important given the fact that patients with Crohn's disease flares are treated with steroids as first-line therapy, which can be detrimental (and fatal) to a patient with an active herpes viral infection of the colon, particularly those with cirrhosis.

References

- Hanauer SB, Meyers S. Management of Crohn's disease in adults. *Am J Gastroenterol*. 1997;92:559-566.
- Banerjee D, Deb R, Dar L, Mirdha BR, Pati SK, et al. High frequency of parasitic and viral stool pathogens in patients with active ulcerative colitis: report from a tropical country. *Scand J Gastroenterol*. 2009;44:325-331.
- Goodell SE, Quinn TC, Mkrtrichian E, Schuffler MD, Holmes KK, Corey L. Herpes simplex virus proctitis in homosexual men. Clinical, sigmoidoscopic, and histopathological features. *N Engl J Med*. 1983;308:868-871.
- el-Serag HB, Zwas FR, Cirillo NW, Eisen RN. Fulminant herpes colitis in a patient with Crohn's disease. *J Clin Gastroenterol*. 1996;22:220-223.
- Naik HR, Chandrasekar PH. Herpes simplex virus (HSV) colitis in a bone marrow transplant recipient. *Bone Marrow Transplant*. 1996;17:285-286.
- Dray X, Treton X, Mazon MC, Lavergne-Slove A, Joly F, et al. Herpes simplex virus type 1 colitis in a patient with common variable immunodeficiency syndrome. *Eur J Gastroenterol Hepatol*. 2006;18:541-544.
- Colemont LJ, Pen JH, Pelckmans PA, Degryse HR, Pattyn SR, Van Maercke YM. Herpes simplex virus type 1 colitis: an unusual cause of diarrhea. *Am J Gastroenterol*. 1990;85:1182-1185.
- Delis S, Kato T, Ruiz P, Mittal N, Babinski L, Tzakis A. Herpes simplex colitis in a child with combined liver and small bowel transplant. *Pediatr Transplant*. 2001;5:374-377.
- Daley AJ, Craven P, Holland AJ, Jones CA, Badawi N, Isaacs D. Herpes simplex virus colitis in a neonate. *Pediatr Infect Dis J*. 2002;21:887-888.
- McBane RD, Gross JB Jr. Herpes esophagitis: clinical syndrome, endoscopic appearance, and diagnosis in 23 patients. *Gastrointest Endosc*. 1991;37:600-603.
- Tomita T, Chiga M, Lenahan M, Balachandran N. Identification of herpes simplex virus infection by immunoperoxidase and in situ hybridization methods. *Virchows Arch A Pathol Anat Histopathol*. 1991;419:99-105.

Review

Herpes Simplex Virus Colitis Complicating the Course of a Patient With Crohn's Disease and Cirrhosis: An Underestimated Association?

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Herpes simplex virus (HSV) colitis is very rare. Only a few cases have been reported in patients with inflammatory bowel disease (IBD), possibly simulating disease relapse.¹⁻⁴ In 2007, Schunter and associates² reported the case of a 35-year-old woman with an exacerbation of ulcerative colitis caused by HSV type 2 (HSV-2) infection who underwent colectomy. Blaszyk and colleagues³ diagnosed HSV colitis via immunohistochemistry of a

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colectomy specimen from a 31-year-old woman who underwent surgery for medically refractory ulcerative colitis. R  ther and coworkers⁴ described the case of a 25-year-old Crohn's disease patient who avoided surgery for a stenosis of the sigmoid colon. HSV-1 and -2 were found in the patient's intestinal mucosa, and the clinical course of the disease was favorable with aciclovir.

Smith and associates⁵ reported a case of HSV colitis occurring in an immunocompromised patient suffering from both cirrhosis and Crohn's disease who required steroid therapy. This report raises important questions regarding the management of refractory IBD in clinical practice such as: What impact does immunomodulator therapy have on the natural history of HSV? Which preventive measures should be adopted? How should the diagnosis be determined? How should the infection be treated?

Primary HSV infection causes an asymptomatic or mild oral labial (usually HSV-1) or genital (usually HSV-2) infection in immunocompetent patients. Subsequently, latent HSV persists in nerve ganglia.⁶ The seroprevalence of both HSV-1 and -2 may be influenced by several factors, including age, gender, and geographic distribution across the world as well as within the same country.⁶ The worldwide prevalence of HSV-1 by the fourth decade is 45–98%.⁶ HSV-2 seroprevalence rises at the beginning of sexual activity in adolescence and increases in adulthood,⁷ with a peak between 15 and 24 years of age and a subsequent decline with advancing age. Cell-mediated immunity is the dominant process for controlling viral replication.⁷ Hence, in immunocompromised individuals, HSV infection has a greater potential for dissemination. Potentially life-threatening systemic infections have been described in the following diseases: encephalitis,^{8,9} meningitis, pneumonia,^{9,10} esophagitis, colitis,^{2,3} or hepatitis. Recurrent oral or genital herpes may also be more severe and more frequent in immunocompromised patients.^{11,12}

As long as no vaccination is available for HSV, the usual protection should be considered in immunodeficient patients. Although different nucleoside analogue therapies are effective for severe HSV infection, the potential for adverse events does not justify standard chemoprophylaxis based upon these medications. In the setting of recurrent labial or genital HSV infection, oral antiviral therapy such as aciclovir 400 mg twice daily should be discussed.¹²

The first consideration one should keep in mind is that the presence of HSV antibodies indicates prior exposure to HSV, but is inadequate for diagnosing active infection. The presence of high titers of anti-HSV immunoglobulin (Ig)G, the appearance of anti-HSV IgM, or the increase of titers of anti-HSV IgG are indicators of relapsing HSV infection. The gold standard for diagnos-

ing HSV infection is polymerase chain reaction (PCR) assay or immunohistochemistry from affected tissue or biopsies.⁶ As HSV colitis is uncommon, the European Crohn's and Colitis Organization (ECCO) does not recommend screening for latent HSV infection in IBD patients even prior to the onset of immunomodulator therapy.¹³ In the setting of HSV symptomatic infection, aciclovir, a nucleoside analogue, is effective.¹² This analogue selectively inhibits the replication of herpes viruses by inhibiting the viral polymerase after intracellular uptake and conversion to aciclovir triphosphate.¹⁴ Valaciclovir, penciclovir, and famciclovir may also be effective in this indication.

According to Listing and associates,¹⁵ discontinuation of immunomodulators or systemic antiviral therapy is not required in HSV infection that occurs during immunomodulator therapy, as most cases of systemic HSV reactivation in immunocompromised patients are self-limited. However, as immunosuppressive therapy may exacerbate HSV infection, immunomodulators should not be initiated during active infection.¹⁶ In severe HSV infection (hepatitis, encephalitis, colitis, or pneumonitis) during immunosuppressive therapy for IBD, intravenous antiviral therapy and discontinuation of immunomodulators are recommended.¹⁴ Smith and colleagues noted that discontinuation of steroid therapy and initiation of antiviral therapy were associated with rapid cessation of abdominal pain and bloody stools. Of note, the patient was receiving immunomodulator therapy, and cirrhosis itself was an immunocompromised condition. Unfortunately, the patient died from hepatic failure.

ECCO recently published its recommendations on the prevention, diagnosis, and management of opportunistic infections in IBD.¹³ Past or latent HSV infection is not a contraindication to immunomodulator therapy (Evidence Level [EL] 2, Recommendation Grade [RG] B).¹³ In the setting of recurrent labial or genital HSV infection, oral antiviral therapy should be considered during immunomodulator therapy (EL 2, RG C).¹³ HSV colitis is best excluded by immunohistochemistry or tissue PCR as a cause of immunomodulatory refractory IBD before increasing immunomodulator therapy (EL 4, RG D).¹³ In the event of severe HSV during immunomodulator therapy, antiviral therapy should be initiated and immunomodulators discontinued until improvement of symptoms (EL 4, RG C).¹³

Cytomegalovirus is routinely researched during IBD relapses. The case reported by Smith and coworkers underscores the need to rule out HSV before boosting immunomodulator therapy. Endoscopy assessment with biopsy should be systematic, and the pathologist should be informed to check for HSV.

References

1. El-Serag HB, Zwas FR, Cirillo NW, Eisen RN. Fulminant herpes colitis in a patient with Crohn's disease. *J Clin Gastroenterol.* 1996;22:220-223.
2. Schunter M, Walles T, Fritz P, Meyding-Lamadé U, Thon K, et al. Herpes simplex colitis complicating ulcerative colitis: a case report and brief review on superinfections. *JCC.* 2007;1:41-46.
3. Blaszyk H, Hyman NH, Cooper K. Herpes simplex virus colitis in ulcerative colitis, simulating malignancy. *Histopathology.* 2006;49:316-318.
4. Rüter U, Nunnensiek C, Müller HA, Rupp W, Gförer S, et al. Herpes simplex-associated exacerbation of Crohn's disease. Successful treatment with acyclovir [in German]. *Dtsch Med Wochenschr.* 1992;117:46-50.
5. Smith JO, Sterling RK, Mills AS, Stravitz RT, Luketic VAC, et al. Herpes simplex virus colitis in a patient with Crohn's disease and hepatitis B and D cirrhosis. *Gastroenterol Hepatol.* 2010;6:120-122.
6. Fatahzadeh M, Schwartz RA. Human herpes simplex virus infections: epidemiology, pathogenesis, symptomatology, diagnosis, and management. *J Am Acad Dermatol.* 2007;57:737-763; quiz 764-766.
7. Gupta R, Warren T, Wald A. Genital herpes. *Lancet.* 2007;370:2127-2137.
8. Alimohamadi SM, Malekzadeh R, Mirmadjless SH, Mohamadnejad M, Zamani F. Herpes simplex virus encephalitis during immunosuppressive treatment of ulcerative colitis. *MedGenMed.* 2004;6:7.
9. Taplitz RA, Jordan MC. Pneumonia caused by herpesviruses in recipients of hematopoietic cell transplants. *Semin Respir Infect.* 2002;17:121-129.
10. Liebau P, Kuse E, Winkler M, Schlitt HJ, Oldhafer K, et al. Management of herpes simplex virus type 1 pneumonia following liver transplantation. *Infection.* 1996;24:130-135.
11. Witt MN, Braun GS, Ihrler S, Schmid H. Occurrence of HSV-1-induced pneumonitis in patients under standard immunosuppressive therapy for rheumatic, vasculitic, and connective tissue disease. *BMC Pulm Med.* 2009;9:22.
12. Fillet AM. Prophylaxis of herpesvirus infections in immunocompetent and immunocompromised older patients. *Drugs Aging.* 2002;19:343-354.
13. Rahier J, Ben-Horin S, Chowers Y, Conlon C, De Munter P, et al. European evidence-based Consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *JCC.* 2009;3:47-91.
14. Whitley RJ, Gnann Jr JW. Acyclovir: a decade later. *N Engl J Med.* 1992;327:782-789.
15. Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. *Arthritis Rheum.* 2005;52:3403-3412.
16. Slifkin M, Doron S, Snyderman DR. Viral prophylaxis in organ transplant patients. *Drugs.* 2004;64:2763-2792.