gone surgical treatment for adenocarcinoma of the transverse colon,[7] and a child who had received a combined liver and small bowel transplant[8]). There has also been a case report of a neonate with congenital HSV infection with hematochezia 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.

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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 associates[2] 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 colleagues[3] 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. Rüther and coworkers[4] 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 associates[5] 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 diagnosing 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.[1,4] 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 recieving 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.

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