SHORT REPORT

Herpes simplex virus colitis complicating ulcerative colitis: A case report and brief review on superinfections

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Abstract In patients with inflammatory bowel disease herpes simplex virus infection has been described as a major cause of morbidity and mortality, especially in immunocompromised individuals. Here we present the case of a 35-year old woman with an exacerbation of ulcerative colitis caused by herpes simplex virus infection (HSV-2). The diagnosis was confirmed histologically following subtotal colectomy. After intravenous treatment with aciclovir for 2 weeks postoperative hematochezia stopped. Herpes simplex virus colitis is a rare but potentially fatal complication of immunosuppressive treatment in patients with inflammatory bowel disease. Prompt diagnosis and efficient antiviral therapy are mandatory to improve prognosis.

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1. Introduction

Herpes simplex virus (HSV) infection is common across the world; worldwide more than 90% of people are seropositive for HSV by the fourth decade of life.1 Primary infection in immunocompetent individuals is characterised by a symptomatic or mild, self-limiting course whereas in immunocompromised patients HSV infection may cause severe infections of different organs with significant morbidity and mortality. If linked to exogenous or endogenous immunosuppression HSV infection is most commonly a result of reactivation.2 Although HSV infection is uncommon in patients with inflammatory bowel disease, treatment with immunosuppressive agents like corticosteroids, azathioprine, cyclosporine, tacrolimus or methotrexate clearly increases infection risk. Ongoing inflammation by itself is also considered to be a predisposing factor for infection with HSV.3-5 Here we describe the case of a female patient with HSV colitis on the background of ulcerative colitis.
2. Presentation of Case

A 35-year old woman with ulcerative colitis diagnosed 5 years before was admitted to our hospital with severe abdominal pain and tenderness, bloody diarrhoea, loss of weight (10 kg within 3 weeks) and increasing fatigue.

Three weeks earlier the patient had been admitted to this hospital because of a severe flare with 15–20 bowel movements a day. At that time a sigmoidoscopy showed a severe active ulcerative rectosigmoiditis. Abdominal ultrasound revealed a thickened colonic wall (Fig. 1). Repeated stool cultures for enteric bacterial pathogens were negative, and serologic assessment as well as biopsies from the sigma and rectum showed no evidence of an infection with cytomegalovirus. Since the disease was refractory to high dose steroids (60 mg prednisolone for 3 weeks) an immunosuppressive therapy with tacrolimus and azathioprine was initiated. During the following days the diarrhoea and the overall condition improved although food intake was still impossible due to malaise.

On day 2 of tacrolimus treatment she developed an acute abdomen with abdominal tenderness and signs of a paralytic ileus. Temperature was 36.9 °C, pulse rate was 115/min and blood pressure was 115/74 mm Hg. The abdominal X-ray showed a massive colonic dilatation (maximum 11.5 cm) reflecting toxic megacolon (Fig. 2). Endoscopic decompression was initiated successfully. Endoscopic examination revealed large ulcers within a destructed bowel wall with spontaneous bleeding (Fig. 3). Laboratory parameters disclosed severe anemia (hemoglobin 65 g/l), hyponatriemia (129 mmol/l) and hypalbuminemia (14 g/l). The C-reactive protein was elevated (6.8 mg/l). All other parameters including liver and kidney function tests were normal.

Blood transfusions were given, parenteral nutrition was initiated via a central venous catheter and an antibiotic treatment consisting of levofloxacin and metronidazole was administered whereupon the patient gradually improved.

On day two after endoscopic decompression the decompression tube was accidentally dislocated. Since colonic dilatation recurred subtotal colectomy with protective ileostomy was performed. Operation revealed a fulminant pancolitis. The rectum was left in situ and was closed (Hartmann situation). The postoperative course was complicated by rectal bleeding requiring rectal tamponade. The histologic-pathological analysis of the colonic resection confirmed severe ulcerative colitis but also showed histological evidence of a viral superinfection with ballooning and opaque infectious bodies (Fig. 4). Immunohistochemistry, using an anti-HSV-2 antibody, detected herpes simplex virus type 2 (HSV-2) in the submucosa of the colon (Fig. 4) whereas CMV was again negative. The polymerase chain reaction (PCR) proved positive for HSV-DNA in the mucosa of the colon. In
the serum HSV IgM and IgG immunoglobulin could be detected which verified a recently acquired HSV infection. An antiviral intravenous therapy with Aciclovir was administered for 2 weeks whereupon the rectal bleeding ceased. Immunosuppressive therapy was aborted and supportive oral iron substitution was administered until hemoglobin levels normalized. In the following oral food intake could be initiated and the patient gained weight quickly. A sphincter manometry showed a nearly physiological sphincter tonus and a later restoration via ileal pouch was planned. Finally the patient could be discharged successfully after 48 days.

Two months later the patient appeared for proctological examination in preparation for a pouch procedure. A severe proctitis with a subtotal stenosis in the upper anal canal was found, which could not be passed even with a pediatric endoscope. The rectal stump had to be resected and a permanent ileostomy was performed.

3. Discussion

This report describes the case of a 35-year old woman with therapy-refractory ulcerative colitis complicated by a herpes simplex (HSV-2) colitis.

Although the pathogenesis of inflammatory bowel disease remains unclear, several studies have suggested that the onset and development of inflammatory bowel disease require the interaction between genetic susceptibility, stimulation by luminal bacterial antigens and adjuvants, and episodic environmental triggers which break the mucosal barrier.6,7

In therapy-refractory and fulminant cases of ulcerative colitis infectious causes have to be kept in mind. Numerous viral and bacterial agents have been associated with complicated or therapy-refractory course of ulcerative colitis especially in immunocompromised patients.

3.1. Viruses Complicating IBD

Several viruses with a facultative intestinal organotropy such as cytomegalovirus,6,9 human parvovirus B19,10 Epstein–Barr virus11 and herpes simplex virus12 have been reported. However, the absolute numbers have not been investigated thoroughly, comparative analyses are lacking so far. Most data rely on case reports or series.

Figure 3 Endoscopic appearance of severe ulcerative colitis. The upper picture shows the mucosa with pseudopolyps. In the lower picture a large fibrous ulcer with deep necrotys is shown.

Figure 4 Histology of colonic specimens demonstrates lymphoplasmocellular infiltrate and opaque inclusion bodies (blue arrows). Immunohistochemistry with anti-HSV2 reveals positive staining of non-endothelial cells as well as possible giant cells (black arrows). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Involvement of the gastrointestinal tract with herpes simplex virus (HSV) is a rare finding in adults but is associated with significant mortality.\(^{13}\)

HSV type 1 (HSV-1) is transmitted by close contact, both homosexual and sexual, and primary infections are usually acquired during childhood and adolescence. Infection with HSV type 2 (HSV-2) is the cause of most genital herpes and is almost always sexually transmitted.\(^1\) Primary infection in immunocompetent individuals is mostly characterised by a symptomatic or mild, self-limiting course whereas in immunocompromised hosts HSV reactivation may cause severe infections of different organs with significant morbidity and mortality like encephalitis, meningitis, pneumonia, gastrointestinal infection and hepatitis.\(^3-5,14\)

HSV esophagitis is the most frequent location for gastrointestinal HSV infection, both in immunocompetent and immunosuppressed hosts.\(^15\) Anorectal herpes is known as a major sexually transmitted infection in patients with AIDS and is usually limited to the distal rectum, whereas extensive HSV colitis is a rare finding in adults.\(^16\) There are only few cases of HSV-caused colitis reported in the literature and all of them were associated with endogenous or exogenous immunosuppression.

Symptoms of HSV colitis are not specific and do not differ considerably from colitis caused by other agents. Watery diarrhoea with addition of blood, crampy abdominal pain, fever, arthralgia, nausea, loss of appetite and loss of weight can be found.\(^17\) Because of the high seropositivity for HSV worldwide, serological analysis plays a minor role in the diagnosis of HSV infection. HSV DNA by polymerase chain reaction (PCR) in colonic biopsies is more reliable. Immunofluorescence staining in colonic tissue with HSV type specific monoclonal antibodies against glycoproteins raises specificity to confirm diagnosis.\(^18\) In the presented case histology disclosed features of viral colitis which was confirmed by positive immunohistochemistry and PCR.

A fast and confident diagnosis of HSV colitis is necessary to start an antiviral therapy without loss of time to decrease mortality. An efficient agent for HSV therapy is the nucleoside analog acyclovir. It selectively inhibits the replication of HSV type 1 and 2 as well as varizella zoster virus (VZV) and Epstein–Barr virus (EBV) by inhibiting viral polymerase after intracellular uptake and conversion to acyclovir triphosphate.\(^19\) Other antiviral substances for the therapy of HSV infection are valacyclovir, a prodrug of acyclovir, penciclovir and its prodrg famciclovir. Unfortunately HSV resistance against acyclovir does include resistance to the other aforementioned agents. The incidence of acyclovir resistance among immunocompromised individuals is higher than in the general population.\(^20,21\)

Unlike HSV colitis superinfection with cytomegalovirus (CMV) is a well recognised phenomenon complicating steroid refractory inflammatory bowel disease. Cytomegalovirus (CMV) can cause a wide variety of infections with significant morbidity and mortality in different organs depending on an immunodeficiency of the host.\(^22\) Primary infection in immunocompetent individuals is often asymptomatic or proceeds as a self-limiting, mononucleosis-like course, whereas reactivation of cytomegalovirus during endogenous or exogenous immunosuppression can result in retinitis, colitis, pneumonitis, hepatitis and encephalitis.\(^23\)

Gastrointestinal infection caused by cytomegalovirus (CMV) has to be suspected in patients with a recognised high risk for CMV infections, such as acquired immunodeficiency syndrome (AIDS) or other immunodeficiency states, transplant recipients, steroid therapy, inflammatory bowel disease, cancer or chemotherapy.\(^8\) Clinical manifestations are oral erosions or ulcers, esophagitis, gastric infection and affection of the small and large intestine.

Gastrointestinal CMV disease in patients with inflammatory bowel disease is rare (0.53%–3.4% but the incidence increases to 15.8%–34% in immunocompromised patients).\(^9\) Esophageal and colonic infection are the most common locations of gastrointestinal cytomegalovirus affection in immunocompromised hosts.\(^24\) Symptoms of colonic CMV disease are diarrhoea, haematochezia, urgency, tenesmus, abdominal pain and constitutional symptoms like fever, malaise and weight loss to the point of anorexia.\(^25\) The course can be complicated by massive bleeding, colonic perforation and a toxic megacolon.\(^26-28\)

In addition to serology, endoscopic examination with histology is necessary to establish the diagnosis of CMV colitis. CMV DNA in colonic tissue can be detected by polymerase chain reaction (PCR). Immunohistochemistry performed on colon biopsies with monoclonal antibody directed against CMV early antigen is suitable to increase specificity and is therefore the gold standard in diagnostic approaches of CMV colitis.\(^29\)

Whereas in immunocompetent individuals supportive therapy of CMV colitis is adequate, hosts with immunosuppression have a high mortality rate and must receive antiviral therapy. Ganciclovir, a nucleoside analogue, inhibits viral DNA polymerase and is an effective agent to treat gastrointestinal CMV disease. Ganciclovir should be given intravenously at a dose of 10–15 mg/kg per day divided in 2 to 3 doses a day for 3 weeks. Ganciclovir therapy was associated with negative cultures within 2 weeks of beginning the treatment.\(^8\)

It is controversially discussed if treatment of CMV superinfection in patients with inflammatory bowel disease enhances the course of disease.

### 3.2. Bacterial Pathogens Complicating IBD

Data from several studies suggest that infection with enteropathogenic microorganisms is associated with the onset and relapse of inflammatory bowel disease. Beside viral agents, bacteria and parasites are supposed to cause initiation and reactivation of ulcerative colitis or Crohn’s disease (Table 1).\(^30\) Colitis associated bacteria identified as pathogens in patients with relapsed or severe inflammatory bowel disease are Salmonella typhi, Yersinia enterocolitica, Campylobacter jejuni, Aeromonas hydrophila, Clostridium difficile, Escherichia coli, Shigella sp. and Staphylococcus aures.\(^31,32\) Clostridium difficile plays a major role in gastrointestinal infections in patients with inflammatory bowel disease as it was the most common agent found in patients with relapse of inflammatory bowel disease combined with a documented enteric infection and accounted for half of the infections.\(^33\)

Clinical manifestation of bacterial-caused colitis is unspecific and can also simulate an acute exacerbation of inflammatory bowel disease. Watery diarrhoea often...
Table 1 Enteropathogenic microorganisms that may cause onset or reactivation of IBD

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Viruses</th>
<th>Parasites</th>
</tr>
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<tbody>
<tr>
<td>Salmonella sp.</td>
<td>Cytomegalovirus</td>
<td>Entamoeba histolytica</td>
</tr>
<tr>
<td>Shigella sp.</td>
<td>Herpes simplex virus</td>
<td>Giardia lamblia</td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Rotavirus</td>
<td>Cryptosporidium parvum</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>Epstein–Barr virus</td>
<td>Schistosoma mansoni</td>
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<tr>
<td>Yersinia sp.</td>
<td>Adenovirus</td>
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<tr>
<td>Aeromonas sp.</td>
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<tr>
<td>Escherichia coli</td>
<td></td>
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<tr>
<td>Staphylococcus aureus</td>
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disease a treatment with metronidazole mostly results in a quick recovery from symptoms.47

4. Conclusion

Herpes simplex virus (HSV) infection should be considered in patients with inflammatory bowel disease in case of failure of conventional treatment or in case of relapse of inflammation. PCR of rectosigmoidal biopsy and immunohistochemical staining of colonic tissue seem to be the most sensible methods for confidential detection of HSV. Fast diagnosis is essential to start appropriate treatment with acyclovir as in this case. However, the risk for colectomy appears to be high.

References


3.3. Parasites Complicating IBD

Several parasite pathogens like Entamoeba histolytica, Cyclosporidium parvum, Giardia lamblia and Schistosoma mansoni were found in patients with inflammatory bowel disease. Enteric parasitic infection can mimic symptoms of inflammatory bowel disease and can trigger onset and relapse of inflammatory bowel disease and might lead to invasive disease during immunosuppression.43,44 Although parasites apparently do not play a major role specimens should be examined to determine the existence of parasites, especially E. histolytica, in cases of refractory course of inflammatory bowel disease.45,46 If infection with parasites is supposed to complicate the course of inflammatory bowel

combined with tenesmus or abdominal pain, nausea, vomiting, headache, fever and myalgia can be found. Usually the clinical course is characterised by a self-limiting course limited to the gastrointestinal tract. Complications and invasive disease are rare but the risk for an extended or complicated course increases in case of an immunosuppression. Complications described previously are metabolic disturbances and dehydration, bacteraemia, endocarditis, pericarditis, myocarditis, myotic aneurysm, osteomyelitis, toxic megacolon, colonic perforation, reactive arthritis and Guillain–Barre syndrome.34–39

In immunocompetent hosts an antibiotic treatment of an uncomplicated bacterial enteritis normally is unnecessary. In patients with an elevated risk such as immunosuppression, elderly and pregnant women or a complicated course antibiotic therapy should be considered to reduce intensity and to shorten symptoms.40 Fluoroquinolones are effective agents for the therapy of enteric infection with Salmonella, Shigella, Yersinia, Aeromonas and E. coli. Alternative antibiotic substances are third generation cephalosporines and in some cases trimethoprim-sulfamethoxazole and antibiotic substances are third generation cephalosporines and in some cases trimethoprim-sulfamethoxazole and chloramphenicol. Drug of choice in therapy of C. jejuni enteritis is erythromycin, alternatives in resistant isolates are tetracyclines or fluoroquinolones.41 First line therapy for pseudomembranous colitis caused by C. difficile is oral metronidazole. Oral vancomycin is an option in case of pseudomembranous colitis caused by C. difficile is oral metronidazole. Oral vancomycin is an option in case of pseudomembranous colitis caused by C. difficile is oral metronidazole.
30. Stallmach A, Carstens O. Role of infections in the manifestation or reactivation of inflammatory bowel diseases. Inflamm Bowel Dis 2002;8:213–8.