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Case report

Herpes simplex infection of the jejunum occurring in the early post-transplantation period

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Summary:

Reactivation of infections with herpes viruses is a frequent and major cause of morbidity after bone marrow transplantation. In this case report we stress that HSV infections of the colon and small intestine should be considered in the differential diagnosis of diarrhea and intestinal bleeding in the early post-transplantation period. Severe acute GVHD and subsequent intensive immunosuppressive treatment may increase the risk for reactivation of HSV infection particularly in situations in which acyclovir prophylaxis has been omitted.
Keywords: HSV; acute GVHD; intestinal bleeding

Reactivation of infections with herpes viruses such as varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), or herpes simplex virus (HSV 1 and 2) is a frequent and major cause of morbidity after bone marrow transplantation. The reactivation of latent persisting HSV occurs in 70% of seropositive patients usually during the first month after BMT.[1] Today, the introduction of prophylactic treatment with acyclovir has significantly decreased the incidence of both localized and systemic infections. Most patients developing clinically apparent disease present with severe oral or genital mucositis and esophagitis. Occasionally, dissemination of HSV can lead to life-threatening encephalitis, pneumonia or hepatitis.[1] Little is known about the role of HSV as a causative agent in infectious enteritis with diarrhea occurring in the early post-transplantation period. Besides a variety of bacterial, fungal and protozoal microorganisms, CMV is the most frequent viral agent responsible for enteritis. HSV infection of the intestine is uncommon.[2] So far only six patients with intestinal HSV infection (colitis in all of the cases) have been reported in the literature.[3–7] We describe a BMT recipient with severe acute graft-versus-host disease who experienced HSV infection of the jejunum which led to serious diffuse mucosal damage and intestinal bleeding.

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Case report

A 27-year-old woman received an allogeneic BMT from her HLA-identical, MLC non-reactive sibling donor for treatment of progressive centroblastic–centrocytic lymphoma (Kiel classification) in relapse refractory to conventional salvage chemotherapy. The patient was CMV antibody negative and HSV antibody positive, and the donor was positive for anti-CMV-IgG and negative for HSV antibodies. The preparative regimen for BMT consisted of busulfan (10 mg/kg), thiotepa (750 mg/m^2) and cyclophosphamide (120 mg/kg). Graft-versus-host disease prophylaxis consisted of cyclosporin A and a short course of methotrexate on days +1, +3, +6 and +11. Acyclovir prophylaxis against herpes virus reactivation was started intravenously on day +1 (3×500 mg daily) and was discontinued on day +19 during a period characterized by deteriorating renal function but concurrent rapid hematopoietic engraftment. Intravenous immunoglobulin was given at 100 mg/kg on days −1, +7, +14 and biweekly thereafter.

She gradually developed grade III acute GVHD involving skin, liver and the intestinal tract, manifesting with profuse watery diarrhea. Day +31 prednisone treatment was initiated with 3 mg/kg i.v. daily. While skin manifestations stabilized, diarrhea worsened. Repeated stool cultures for bacteria, *Clostridium difficile* toxin and fungi were negative. Consecutively, prednisone was increased to 15 mg/kg i.v. for 3 days and subsequently rapidly tapered when GVHD had improved to grade II. However, on day +45 the diarrhea recurred and was associated with massive blood loss, requiring transfusion of 8 units of packed red blood cells. Endoscopy was performed to localize the source of blood loss. The colon and stomach were unremarkable, whereas the duodenum was heavily diffusely inflamed but not bleeding. At that time, as no oral or nasolabial ulcerations were present, oral cultures were not performed. Because of continuing blood loss from the jejunum as identified by digital subtraction angiography she was operated on day +50. The jejunum was massively inflamed and bleeding diffusely; 14 cm of jejunum comprising the most affected area were resected. After only transient clinical improvement the patient died of uncontrolled intestinal bleeding on day +57.

Microscopic examination of the surgical specimen revealed necrosis of the entire mucosa (with no specific

cell alterations such as inclusion bodies identifiable). The submucosal layer was edematous, consistent with acute GVHD grade IV. Further immunohistochemical examination with a polyclonal antibody showed patchy areas of positivity for HSV antigens in the mucosal cells. The antibody used does not discriminate between HSV 1 and HSV 2 (Figure 1). PCR analysis for HSV 1 and HSV 2 was performed using a triple oligo PCR with three primers localized in the DNA polymerase region of the HSV 1 and HSV 2 genome. Amplification of different sized fragments allows discrimination between HSV 1 and HSV 2. Whereas weekly PCR analysis of buffy coat and serum remained negative for HSV 1 and HSV 2 throughout the clinical course, analysis of the jejunal biopsy and jejunal irrigation fluid revealed positivity for HSV1 and negativity for HSV 2. It is of note that CMV infected cells could not be demonstrated and PCR analyses of buffy coat lysates were negative for CMV DNA throughout the total post-transplant period.

Discussion

In this case report we describe a patient with HSV 1 infection of the jejunum leading to diarrhea and death from uncontrolled intestinal bleeding. A literature search revealed six case reports about patients with HSV-associated infection of the intestine.[3–7] However, in all of the patients reported colitis was diagnosed but the small intestine was never affected. A common underlying problem in these patients was disturbance of the immune defense. One patient was a kidney transplant recipient, another suffered from Hodgkin's disease being treated with C-MOPP, a further patient was an HIV-positive homosexual man with opportunistic infections. Only one patient was a bone marrow transplant recipient as our case. It is debatable, however likely, that the sixth patient, a 78-year-old woman, also had an impaired immune system. It is of note that three of the six patients showed additional general mucosal ulcers on the perineum, external genitalia, oral cavity or penis.

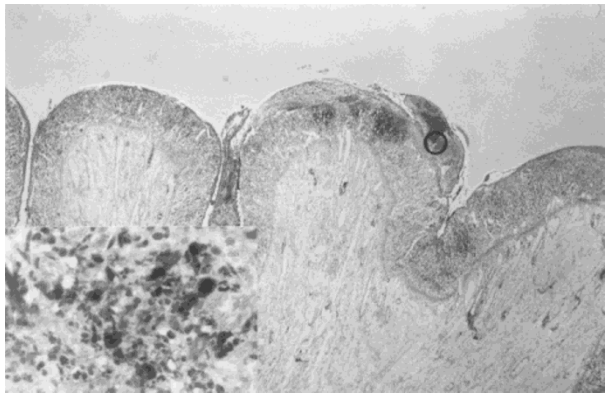

Figure 1 Positive nuclear staining with antibody against HSV (rabbit-anti-HSV, DAKO, Hamburg, Germany) in the submucosal layer in necrotic areas of the jejunum (APAAP × 15, 75, insert APAAP × 220).

Early after BMT the occurrence of diarrhea is a common complication caused either by the conditioning therapy, antibiotic treatment, GVHD, or by infections with various microorganisms. Fifty percent of patients with grade II to IV acute GVHD have gastrointestinal involvement[8] which may lead to bleeding from the small intestine and the colon if extensive ulceration of the mucosa is present. Patients presenting with intestinal bleeding due to acute GVHD of the intestine have concurrent CMV infection in about half of the cases.[9] The close correlation of severity of GVHD, immunosuppressive treatment and the occurrence of CMV infection has been described by several groups, whereas such a correlation is less well documented for HSV. There has been a report that donor seropositivity for HSV is associated with a higher incidence of grade II–IV GVHD.[10] One BMT patient presented with GVHD and concomitant HSV-, CMV- and *Clostridium difficile* infection of the colon.[7] HSV was grown from cecal biopsy cultures, but could not be confirmed by histopathology. As in our case, the clinical picture in this patient was complicated by the fact that GVHD was also present.

Since reactivation of latent HSV infections after BMT is a well known phenomenon, patients routinely receive prophylactic treatment with acyclovir. Acyclovir administration in our patient was stopped 3 weeks after BMT, and 2 weeks after BMT in the patient described in Ref. 7, which may have facilitated HSV reactivation. In situations of HSV reactivation where continuing acyclovir prophylaxis is underway, development of acyclovir resistance has to be considered.

In conclusion, HSV infections of the colon as well as the small intestine may cause or contribute to the development of diarrhea in the early post-transplant period. Risk of reactivation appears to be increased during severe acute GVHD and the attendant immunosuppressive treatment and in situations where acyclovir prophylaxis has been omitted or interrupted.

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