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Seronegative *Herpes simplex* Associated Esophagogastric Ulcer after Liver Transplantation

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Key Words
Herpes simplex · Immunosuppression · Liver transplantation

Abstract
Herpes simplex infection is characterized by acute or subacute infection, often followed by a chronic carrier state. Consecutive recurrences may flare up if immunocompromise occurs. *Herpes simplex* associated esophagitis or duodenal ulcer have been reported in immunocompromised patients due to neoplasm, HIV/AIDS or therapeutically induced immune deficiency. Here we report the case of an HSV-DNA seronegative patient who developed grade III dysphagia 13 days after allogeneic liver transplantation. Endoscopy revealed an esophageal-gastric ulcer, and biopsy histopathology showed a distinct fibroplastic and capillary ulcer pattern highly suspicious for viral infection. Immunohistochemistry staining revealed a distinct nuclear positive anti-HSV reaction. Antiviral therapy with acyclovir and high-dose PPI led to a complete revision of clinical symptoms within 48 h. Repeat control endoscopy after 7 days showed complete healing of the former ulcer site at the gastroesophageal junction. Although the incidence of post-transplantation *Herpes simplex* induced gastroesophageal disease is low, the viral HSV ulcer may be included into a differential diagnosis if dysphagia occurs after transplantation even if HSV-DNA PCR is negative.

Introduction

HSV infection is a well-known, chronic persistent viral infection of varying recurrence rate [1]. It has been reported that HSV can be the cause of esophagitis, as seen in immunodeficient patients under therapeutic immunosuppression [2, 3]. Although the risk of a HSV infection appears to be correlated to a degree of depression of the cellular

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immune system, HSV infection is a rare condition after organ transplantation and consecutive immunosuppression therapy. HSV manifestations after transplantation have been described; however, usually a time delay between organ transplantation and HSV infection – corresponding with the time necessary for the achievement of full therapeutic immunosuppression – is seen. The herpes virus group consists of the *Herpes zoster* virus and the *Herpes simplex* virus [1, 4], the former occurring much more often as a painful post-transplant infection [5–7]. Infections or recurrences of HSV after transplantation are much more uncommon and comprise case reports describing esophagitis and nephritis [8, 9]. HSV manifestations as esophagitis are extremely rare; they have been seen in singular cases after kidney [8–10], liver [11], heart [12] and bone marrow transplant [13]. It was Itoh et al. who investigated the relationship between histopathological features and HSV associated esophagitis after transplantation. Reporting on 1,307 autopsies covering a 10-year period, they detected a prevalence of 1.4% (14 out of 1,307) [7]. A HSV related ulcer of the gastroesophageal junction after transplantation has not been reported so far. We describe the very rare case of a seronegative *Herpes simplex* induced ulcer occurring in the early postoperative phase after liver transplantation.

Case Report

Patient History and Surgery

A 64-year-old man with a cryptogenic Child Pugh C liver cirrhosis suffered from hepatic encephalopathy, massive ascites, splenomegaly and consecutive thrombocytopenia and anemia. Thus he underwent allogeneic orthotopic liver transplantation. It was realised by primary biliary anastomosis and temporary insertion of a biliary drain.

On postoperative day 1 diffuse bleeding mandated relaparotomy, further complicated by systemic coagulopathy and transfusion requirements of 44 units of RPC, 118 units of FFP and 12 units of thrombocytes. A consecutive abdominal compartment syndrome and a hepatorenal syndrome necessitated haemodialysis for 5 days, during which programmed relaparotomies and abdominal washouts were performed. At day 10, the patient recovered without further sequelae and was transferred to the regular ward. Enteral feeding was started and increased to a full diet. At postoperative day 17 the patient reported dysphagia for liquids and solids without pain on swallowing, nausea and vomiting. On esophagogastroduodenoscopy a huge ulcer situated at the gastroesophageal junction was discovered as well as moderate gastritis with normal duodenum mucosa (**fig. 1**).

Histopathology

The histopathological examination of biopsies taken from the border and center of the ulcer showed epithelial lesions rich in fibroblasts and capillaries which were highly suspicious of viral infection. Additionally, there were fibrin deposits related to granular sites. The picture was enlarged by megacaryocytes with large lobulated nuclei showing milk glass foggy karyoplasm. On immunohistochemical analysis a distinct positive reaction for NTB-HSV antibodies was seen (**fig. 2**).

Histopathological and immunohistochemical examinations showed a squamous cell epithelium with focal exasperated HSV loci without any sign of neoplasia. Immediate systemic antiviral therapy was started with acyclovir (15 mg/kg/day) plus high-dose PPI (esomeprazole) (50 mg twice a day) led to a complete remission of all clinical gastrointestinal symptoms within 48 h. The following course was uneventful; repeated endoscopy seven days later revealed a complete remission of the previous ulcer of the gastroesophageal junction. The patient was discharged in good health to the outpatient department with a good hepatorenal function.

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Discussion

HSV infection is a common and life-long infection; it may recur at any time as a reaction to different stimuli [1]. HSV-1 recurrences are more often described as compared to HSV-2 recurrences [14]. The possible association between HSV-1 infection and duodenal ulcer in immunocompromised patients has been described before [14]. Up to now, esophageal or esophagogastric ulcers following therapeutic immunosuppression have not yet been described. This is more than surprising, taking into account reports which describe HSV esophagitis after kidney transplantation [9], allogeneic liver transplantation [11], heart transplantation [12] and bone marrow transplantation [13]. As Bissig et al. [11] report HSV hepatitis 4 years after transplantation, it could be speculated that ulceration would occur during the same period mentioned. Nevertheless, we report the case of a HSV ulcer of the gastroesophageal junction 17 days after allogeneic liver transplantation, which was diagnosed by endoscopy, histopathology and immunohistochemistry. It is known that HSV infections can occur in immunocompromised patients and lead to concomitant seropositivity. While in these patients preventive acyclovir medication may be applied, our patient had not been diagnosed with HSV infection before and was HSV-PCR negative. Thus preventive acyclovir was not considered. Antiviral medication was started in our patient from the date of confirmation of the HSV infection on.

In general, HSV reactivation can complicate the postoperative course of immunocompromised patients [12]. It has been known that patients with combined hepatorenal dysfunctions have an increased risk for reactivation of HSV [4]. Furthermore, CD4+/CD8+ depleted patients with liver cirrhosis have an increased risk for HSV recurrence [5–7]. Prophylactic antiviral medication can be chosen at least in patients at risk for CMV infection. Late infectious sequelae may thus be avoided, while costs and drug side effects may simultaneously increase.

In our patient we report the early postoperative reactivation of HSV, leading to ulcer in an uncommon place. This might be due to a combination of hepatorhinorrhagia and massive transfusion which may have led to profound immunosuppression in our patient, although therapeutic immunosuppression was shown to be within therapeutic range. The massive bleeding may have led to the depletion of CD4+/CD8+ cells in our patient, which further added to the immunocompromised state. It cannot be excluded that intraoperative hypotension and systemic catecholamine application added to a mucosal hypoperfusion state with impaired microcirculation, thus increasing the vulnerability of the gastroesophageal junction. This may have led to a locally reduced immune surveillance in the gastrointestinal tract, which is regularly exposed to local microtraumata and infectious agents. We could not identify any causative factor leading to the lesion in the esophagus – nor elsewhere in the gastrointestinal tract.

It is not known whether H2 blocking agents improve the healing in uncomplicated HSV ulcers. We feel that especially patients on steroids need mucous protection, thus the drug doses of PPI were doubled with diagnosis of HSV ulcer. Nevertheless, despite massive transfusion, immunocompromised situation and programmed relaparotomies, the patient recovered without sequelae, even in terms of immunocompetence. The single ulcer found at the gastroesophageal junction was the only expression of HSV reactivation. No further systemic complications occurred.

It was macroscopically impossible to deduce the HSV infection from the ulcer visualized on endoscopy. Astonishingly polymerase chain reaction revealed a negative

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serum anti-HSV titre pre- and postoperatively. Thus the herpes ulcer diagnosis was made by immunhistochemistry of the biopsy specimen alone.

This case report demonstrates that even in the early postoperative phase after transplantation, HSV ulcer of the gastroesophageal junction can occur. Herpes ulcer, although very uncommon, must be added to the differential diagnosis in early postoperative ulcers of the gastroesophageal junction in immunocompromised patients. Fast diagnosis and targeted therapy may lead to a full and unproblematic recovery, as seen in this patient. As it may be difficult to confirm a HSV lesion by serum sample analysis alone, we recommend to take a biopsy specimen for further immunhistochemistry.

Conflict of Interest

All authors certify that they have no commercial association that might pose a conflict of interest in connection with the submitted article, and disclose any financial and personal relationship with other people and organisations that could influence their work.

Fig. 1. First diagnostic proof of HSV induced lesion.

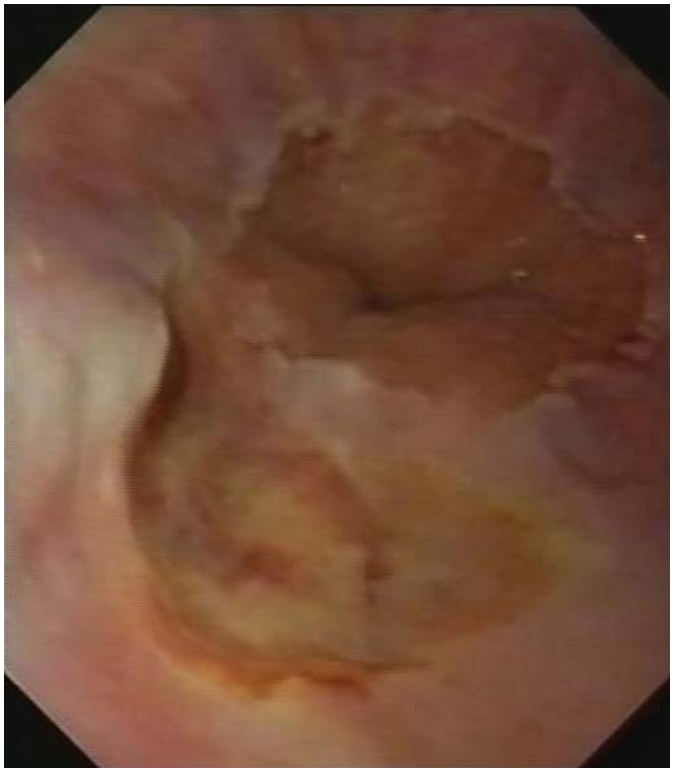

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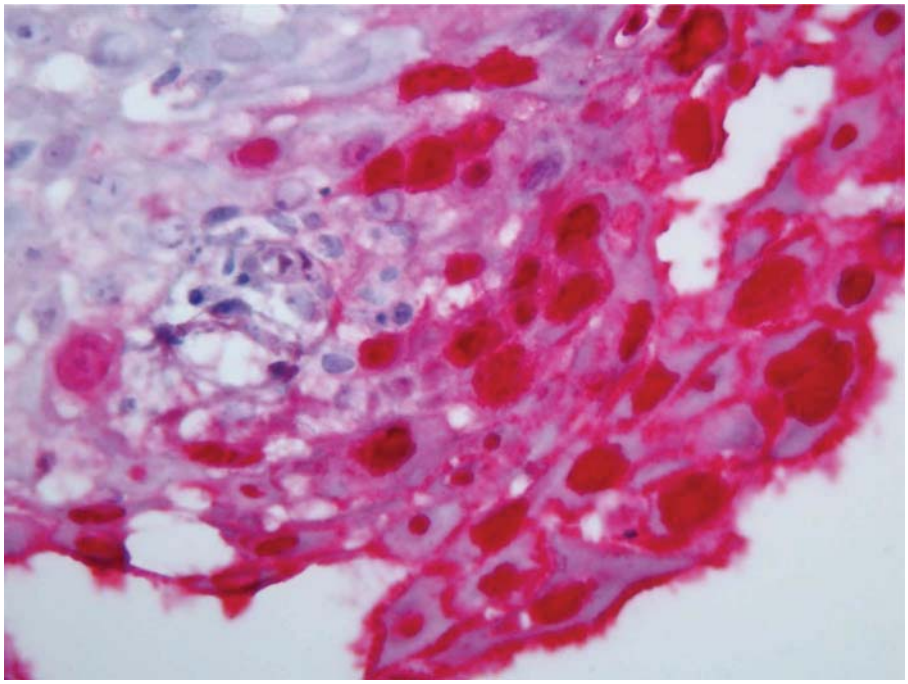
Fig. 2. Immunohistology staining with anti HSV antibodies reveals potent spots within esophageal squamous cells (red areas); 1:400 magnification.



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