Short Report

Herpes Simplex Virus Sepsis in a Young Woman with Crohn’s Disease

Lea-Maxie Haag, a Jörg Hofmann, b Lea Isabell Kredel, c Christina Holzem, d Anja A. Kühl, e Eliane T. Taube, f Stefan Schubert, g Britta Siegmund, h Hans-Jörg Epple i

a Medical Department 1, Charité Universitätsmedizin Berlin, Berlin b Institute of Virology, Campus Charité Mitte, Charité Universitätsmedizin Berlin, Berlin c Medical Department 1, Charité Universitätsmedizin Berlin, Berlin d Medical Department 1, Charité Universitätsmedizin Berlin, Berlin e Medical Department 1, Charité Universitätsmedizin Berlin, Berlin f Institute of Pathology, Campus Charité Mitte, Charité Universitätsmedizin Berlin, Berlin g Gastroenterologie am Bayernischen Platz, Berlin h Medical Department 1, Charité Universitätsmedizin Berlin, Berlin i Medical Department 1, Charité Universitätsmedizin Berlin, Berlin

Corresponding author: Lea-Maxie Haag, MD, Medical Department 1 [Gastroenterology/Infectious Diseases/Rheumatology], Charité Universitätsmedizin Berlin, Campus Benjamin Franklin, Hindenburgdamm 30, DE – 12200 Berlin. Tel.: +49-30-450-514 342; fax: +49-30-450 514 990; email: lea-maxie.haag@charite.de

Abstract

We present the case of a herpes simplex virus-1 [HSV-1] sepsis with severe herpes hepatitis in a young female treated with triple immunosuppressive therapy [adalimumab, azathioprine, prednisolone] for refractory Crohn’s disease [CD]. The patient presented with high fever, generalised abdominal tenderness, strongly elevated transaminases, coagulopathy, and pancytopenia. Comprehensive diagnostics including blood HSV-1 polymerase chain reaction [PCR], liver biopsy, and immunohistochemistry revealed the diagnosis of fulminant herpes hepatitis. HSV-1 positivity of cutaneous lesions proved the disseminated nature of the infection. Early treatment with intravenous acyclovir led to a rapid improvement of the patient’s condition and resulted in a full recovery of her liver function. This is the first reported case of HSV-sepsis in a patient with CD. Physicians treating inflammatory bowel disease [IBD] patients with combined immunosuppressive therapy should be aware of the possibility of herpes hepatitis, and early empirical antiviral therapy should be considered in immunosuppressed patients presenting with fever and severe anicteric hepatitis.

Keywords: Crohn’s disease; inflammatory bowel disease; herpes simplex virus

1. Introduction

Herpes simplex is a rare cause of fulminant hepatitis and a dangerous infectious complication associated with a poor prognosis if not treated properly. We report the case of a HSV-sepsis with severe herpes hepatitis in a young female treated with triple immunosuppressive therapy because of refractory Crohn’s disease [CD].

2. Case report

In March 2014, a 19-year-old woman presented to our emergency department with a 5-day history of fever up to 39.4 °C, abdominal pain, and progressive malaise. In July 2012, the patient had been diagnosed with colonic CD. In December 2013, while on azathioprine [AZA] maintenance therapy, she had developed a severe flare followed by a steroid-refractory course. Thus in February 2014, adalimumab therapy [induction dose 160 mg] and a cotrimoxazole prophylaxis was initiated in addition to the ongoing AZA and prednisolone medication, the latter of which was tapered after adalimumab induction. At the time of admission, the immunosuppressive therapy consisted of adalimumab [second dose, 80 mg, administered 4 days before admission], prednisolone [25 mg], and AZA 150mg.
On examination, the patient was in poor general condition. The temperature was 39.4 °C, the blood pressure 110/80 mmHg, the heart rate 100 beats per min and oxygen saturation 98%. There was generalised abdominal tenderness. In particular, there were no skin or mucous membrane lesions. Laboratory tests revealed strongly elevated transaminases [aspartate aminotransferase [AST] 2659 U/l], alanine aminotransferase [ALT] 1553 U/l], whereas bilirubin and γ-glutamyltransferase [GGT] where within normal limits. Plasma coagulation was slightly prolonged [international normalized ratio [INR] 1.27]. The blood count showed a pancytopenia [leucocytes 0.8 x/nl, thrombocytes 126/ nl, haemoglobin level 11.8 g/dl]. C-reactive protein [CRP] was only marginally increased [5.6 mg/l].

On admission, all medications—except for prednisolone—were stopped and a panel of blood tests was sent for analysis. As the patients’ medication history revealed an intake of acetylsalicylic acid before admission, a continuous infusion of N-acetylcysteine was initiated to prevent acetylsalicylic acid-induced liver failure. The infusion was stopped 24 h later, when acetylsalicylic acid was found to be undetectable in the initial blood tests. Serological tests for hepatitis viruses A, B, C, and E were negative except for anti-hepatitis B antibodies [775 U/l] consistent with previous hepatitis B vaccination. In addition, polymerase chain reaction [PCR] was negative for hepatitis B, C, E virus, cytomegalovirus, and Epstein Barr virus. Auto-antibodies including antinuclear antibody [ANA], anti-smooth muscle antibody [ASMA], antimitochondrial antibody [AMA], antinuclear antibody [ANA], antihistone microsomal antibody [LKM], and antibodies against soluble liver antigens [anti-SLA] were not detectable. Urinary copper excretion as well as serum coeruloplasmin and copper concentrations revealed normal results. Blood and urine cultures were negative, a chest X-ray was unremarkable. An abdominal ultrasound showed no evidence of acute or chronic hepatic disease. Doppler ultrasound demonstrated normal blood flow within the liver veins and the hepatic portal system. An abdominal contrast-enhanced computed tomography [CT] scan confirmed these findings.

One day after admission, worsening liver function tests and coagulopathy [INR 1.57] implied progressive hepatic cytolysis. Therefore, extended diagnostic measures were taken including transjugular liver biopsy and a blood PCR for herpes simplex virus DNA. When the latter proved to be strongly positive [3.5 x 10^9 copies/ml], intravenous acyclovir [15 mg/kg/8 h] was started immediately. Liver biopsy revealed massive hepatic necrosis surrounded by a sparse granulocytic and lymphocytic infiltration [Figure 1a]. Immunohistochemistry demonstrated the strong presence of herpes simplex virus-1 [HSV-1] antigen confined to areas of hepatic necrosis [Figure 1b, c]. Thus, the diagnosis of fulminant herpes hepatitis was established.

Two days after initiation of antiviral therapy, AST levels peaked at 3320 U/l. Four days after admission, small circular erosions occurred at the extremities [Figure 2]. A smear from the cutaneous lesions was positive for HSV-1-DNA, indicating systemic herpes infection. After 6 days of acyclovir therapy, the patient became afebrile and her condition improved continuously. Liver enzymes decreased gradually over time, paralleled by a stabilisation of the plasma coagulation [Figure 3]. After 2 weeks of intravenous therapy, the patient was switched to valacyclovir [2 x 1000 mg per day] and was discharged. After 2 more weeks of oral therapy, the treatment was tapered to 2 x 500 mg valacyclovir as prophylaxis. At that time, liver function tests and complete blood count were normal and herpes plasma virus concentrations had become undetectable [Figure 3]. A colonoscopy 2 months after discharge showed very little inflammation. The patient did not show any symptoms, and a bridging therapy with budesonide was initiated.

3. Discussion

We report the case of a HSV sepsis with severe herpes hepatitis in a young female treated with triple immunosuppressive therapy because of refractory CD. Although hepatitis was the prominent clinical manifestation, a diagnosis of HSV-1 sepsis can be made according to the criteria of the European Society of Intensive Care Medicine based on the combination of a systemic inflammatory response syndrome, a positive blood PCR, and thrombocytopenia. Moreover, cutaneous lesions positive for HSV-1 proved the disseminated nature of the herpes infection. Fortunately, early treatment with intravenous acyclovir led to a rapid improvement of the patient’s condition and resulted in a full recovery of her liver function.

Herpes simplex is a rare cause of fulminant hepatitis. If not recognised early, it often takes a dramatic and fatal course. Unfortunately, the diagnosis of HSV-1 hepatitis is difficult to establish owing to its non-specific clinical features which include high-grade fever, leucopenia, and a marked rise of serum transaminase levels. The absence of hyperbilirubinaemia in an otherwise severe hepatitis may represent the most characteristic finding. Apart from that, all symptoms are shared with other, more prevalent infectious complications. Moreover, as in our patient, typical mucocutaneous herpetic lesions are absent in over 70% of cases. Diagnosis is often delayed and therefore a poor prognosis is associated with the disease. In some case series, an associated mortality of > 80% was reported.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Liver biopsy. [A] Haematoxylin and eosin stain (original x 100) of the liver biopsy with necrosis (eosinophilic area at the underpart). [B] Immunohistochemical staining of herpes simplex virus [HSV-1] antigen [brown] reveals massive positivity in necrotic area (original x 100). [C] Immunohistochemical staining (of HSV-1 antigen [brown]) reveals focal inflammation with presence of HSV-1 antigen in the nuclei and cytoplasm of hepatocytes.
However, there is evidence that early initiation of antiviral treatment significantly improves survival.\textsuperscript{4,5}

Serum PCR, typically showing high copy numbers of herpes simplex DNA, can serve to establish the diagnosis.\textsuperscript{2,5} Therefore, HSV-PCR should be performed in immunocompromised patients presenting with severe acute anicteric hepatitis. Additionally, as immunohistochemical detection of herpes antigen is regarded the diagnostic gold standard, liver biopsy should be considered early in the course of the disease.

As outlined above, the fulminant nature of HSV hepatitis calls for early treatment. Therefore, empirical acyclovir therapy should be initiated if HSV hepatitis is suspected, while diagnostic results are pending [Figure 4].\textsuperscript{2} Acute hepatitis is not a common manifestation of HSV infection. Predisposing factors are impaired cellular immunity due to immunosuppressive therapy, malnutrition, pregnancy, malignancy, or other causes.\textsuperscript{2} As a consequence of immunosuppressive agents, patients with inflammatory bowel disease [IBD] carry an increased risk for opportunistic infections.\textsuperscript{7,4} Still, most cases of HSV infection in IBD patients are mild, and do not require systemic antiviral therapy or a discontinuation of immunosuppressive therapy.\textsuperscript{7,8,9,10,11,12,13,14} However, severe outcomes have also been reported, including encephalitis, pneumonia, and two cases of hepatitis.\textsuperscript{15,16,17,18,19,20} Immunosuppressive therapy raises the risk for infection, especially when given in combination. In a prospective study, AZA was found to increase the risk for benign herpes flares independently of concomitant use of steroids or biological.\textsuperscript{7} On the other hand, the individual risk for steroids is difficult to assess because they are given in combination with other maintenance drugs in most cases. According to the European Guidelines of opportunistic infections in IBD, the risk for infection in patients taking corticosteroids seems to be increased if the daily intake of exceeds a prednisolone equivalent \( \geq 20 \text{mg} \) for more than 2 weeks.\textsuperscript{21} As to the use of biologicals, a recent meta-analysis concluded that they increase the risk of opportunistic viral infections in patients suffering from CD, although a higher frequency of HSV infection was not reported.\textsuperscript{20,22} Therefore, European guidelines presently do not recommend screening for HSV infection before initiation of an immunosuppressive therapy in IBD patients.\textsuperscript{23} Furthermore, serological evidence of HSV infection is not considered a contraindication for immunosuppressive therapy. Notwithstanding the aforementioned guidelines, oral suppressive therapy should be considered in specific cases including patients showing recurrent oral or genital HSV infection. In the case

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\includegraphics[width=\textwidth]{figure2.png}
\caption{Example of small circular erosion detected at the lower extremities 4 days after admission.}
\end{figure}

\begin{figure}
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\includegraphics[width=\textwidth]{figure3.png}
\caption{Kinetics of laboratory parameters. Liver enzyme levels in blood are expressed as x-fold of the upper limit of normal [ULN]. Plasma viral load of herpes simplex virus [HSV] was quantified by quantitative polymerase chain reaction [PCR] as genome copies per millilitre [secondary axis]. Qualitative detection of HSV genome in tracheal secretion [TS] [1 day after admission] and in swabs from skin [arm] and vagina [both obtained 10 days after admission] is depicted in the upper panel. Additionally, prothrombin values are given in % [normal range 70–130%].}
\end{figure}
of clinical suspicion of HSV colitis due to a refractory disease manifestation, HSV infection should be excluded before escalating the immunosuppressive therapy. If HSV infection occurs during immunosuppressive therapy, initiation of an antiviral therapy is recommended and the immunosuppressive drugs are to be discontinued until the improvement of symptoms.

To the best of our knowledge, this is the first reported case of a HSV sepsis in a patient with a previously diagnosed CD and is only the third case of HSV hepatitis in a patient with IBD. Despite its rarity, in patients with impaired immunity herpes hepatitis represents a dangerous infectious complication associated with a poor prognosis if not treated properly. Physicians treating IBD patients with combined immunosuppressive therapy should be alert to the possibility of herpes hepatitis in their patients and be familiar with the clinical picture and management [Figure 4]. In immunosuppressed patients presenting with fever and severe anicteric hepatitis, early initiation of empirical antiviral therapy should be considered.

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**Conflict of Interest**

None.

**Author Contributions**

LMH has made substantial contributions to conception, acquisition, analysis, and interpretation of data and drafting the manuscript. LIK and CH have made substantial contributions to acquisition of data. AAK, SS, and EET have made substantial contributions to analysis and interpretation of data. JH and HJE have made substantial contributions to conception and analysis and interpretation of data as well as revising the manuscript critically. BS has made substantial contributions to conception, acquisition and interpretation of data, as well as revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

**References**


