Case report

Herpes simplex virus load to monitor antiviral treatment after liver transplantation for acute herpetic hepatitis

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Introduction

Acute herpes simplex virus (HSV) hepatitis is a rare cause of acute liver failure (ALF), with only 148 reported cases [1–8]. Because of the poor prognosis it has been suggested to initiate specific antiviral therapy as soon as HSV hepatitis is suspected, while waiting for virological confirmation [9]. Liver transplantation (LT) has been reported in only nine cases for acute HSV hepatitis, with a poor post-transplant survival, as only one-third survived the first year [5,8]. Recurrence of HSV infection in the allograft is a particular concern with uncertainties remaining for both duration and dose of the antiviral treatment. Prolonged antiviral therapy has been suggested to promote emergence of resistant strains that subsequently could lead to recurrence in the allograft [10]. As a consequence, the post-transplant management of such cases is particularly difficult. We report the rare case of a primary HSV-1 hepatitis in an immunocompetent host leading to ALF and LT, and describe the use of HSV viral loads to monitor the effectiveness of the post-transplant antiviral treatment.

Case report

A 64-year-old male was admitted for fever, abdominal pain and stomatitis, in the absence of cutaneous lesions. The evolution was remarkable for pancytopenia, acute renal failure and rapid development of ALF with profound encephalopathy requiring LT. No predisposing immunosuppression was detected. A large screening for viral infections (including hepatitis A, B and C viruses, HIV, cytomegalovirus, Epstein–Barr virus and parovirus B19), as well as toxic causes (paracetamol) and autoimmune diseases (antibodies against S-M2, S-LKM1, S-LC1, S-SLA and S-actine) was negative. Liver histopathology revealed important necrosis surrounded by hepatocytes with intranuclear inclusions (Figure 1A). Immunohistochemistry was positive for HSV-1-2, in the absence of specific immunoglobulin (Ig)M and IgG (Figure 1B). HSV-1 DNA was positive at 64.5 million copies/ml plasma using a type-specific TaqMan real-time PCR previously shown to detect between 10 and 100...
Figure 1. Liver biopsy

(A) The recipient’s pre-transplant liver biopsy shows marked necrosis with disappearance of the normal tissue architecture. Intranuclear inclusions are seen in numerous hepatocytes (hematoxylin and eosin, original magnification ×400). (B) Immunohistochemistry staining for herpes simplex virus-1-2 is positive both for nuclear and cytoplasmic viral inclusions (original magnification ×600).

Discussion

Including our case, 149 cases of HSV hepatitis have been reported so far. This infection is a rare cause of ALF. Indeed a large study including 360 cases of ALF reported that HSV accounted for only 1.4% of them [9]. Most of these cases occurred during primary infections. Herpetic hepatitis is more frequent during infections in immunocompromised hosts. Indeed 80 out of the 149 (54%) published cases occurred in immunocompromised patients, and 45 of them in solid organ transplant recipients. HSV-2 was responsible for 62% of cases [1–8]. Interestingly, the present patient had no apparent immunosuppression and, in the absence of specific IgM and IgG, we retained the diagnosis of primary infection, despite his advanced age. Whether severe cases such as our patient, without apparent immunosuppression, have an unknown immunological defect including polymorphisms in Toll-like receptors (TLR) remains speculative [12]. Indeed both TLR2 and TLR9 have been recently identified as responsible for the innate immune response to HSV, however, so far, the lack of TLR signalling has not been associated with an increase in HSV replication [13,14].

The global reported prognosis of acute herpetic hepatitis is poor; indeed 55% of cases (82/149) were diagnosed at autopsy. This might be due to late suspicion of the disease and delayed specific treatment. If herpetic
hepatitis is suspected, treatment should be promptly initiated. Liver transplantation for HSV hepatitis was performed in 10 cases including our patient [5,8] and 6 of them died within the first year, which compares badly to the 85% expected 1-year survival after LT [15]. However, in only one case was death considered related to recurrent HSV infection and multi-organ failure [10]. Moldovan B et al. [16], based on the Scientific Registry of Transplant Recipients (USA), recently reported a better recovery in children than in adults both prior and post-LT for HSV hepatitis. HSV likely reaches the liver by haematogenous spread, but the factors determining HSV viraemia are poorly understood. HSV viraemia appears to be limited to primary HSV infections and more frequent during herpes genitalis, with up to 50% of patients having detectable HSV DNAemia at that time [17]. As a consequence, it has been suggested that blood donors with primary HSV infection should be excluded from donation. In one small series of liver transplant recipients for herpetic hepatitis, HSV DNA or HSV culture was positive from blood samples at admission in three out of five cases, but viral DNA quantification was not performed [9]. So far, a correlation between hepatic replication and HSV DNAemia has not been established. Clinical implications of HSV viraemia have just recently started to be investigated. In a retrospective study, hepatitis was the most frequent clinical finding in patients with HSV viraemia [18]. The same study reported an extremely wide range of blood HSV DNAemia (from $8.1 \times 10^1$ to $2.6 \times 10^9$ HSV copies/ml) in patients with disseminated infection. In the case presented here, the initial HSV viral load was very elevated ($64.5 \times 10^6$ copies/ml), probably reflecting high viral load during acute primary infection.

In LT recipients for HSV hepatitis, recurrence of HSV viraemia with allograft infection is a major concern. Therefore, long-term suppressive antiviral therapy has been proposed [7,19]. In our case, the viral load rapidly decreased following transplantation and initiation of specific antiviral treatment, and stayed undetectable suggesting efficient long-term suppression of viral replication by valacyclovir (Figure 2). Whether a positive pre-transplant HSV DNAemia, despite antiviral treatment, should influence the timing of LT is unclear. Indeed several published cases, including our case, showed a significant reduction of viral load post-LT [8]. These observations suggest that the removal of the infected liver, being a major reservoir for HSV, might be highly effective in

![Figure 2: HSV-1 DNA plasma load and antiviral therapy](image-url)
reducing the viral load, arguing against delaying LT once indicated [8]. Interestingly, post-LT extrahepatic HSV disease during acyclovir treatment, and despite undetectable viraemia, has been described [8]. This also occurred in our patient, leading to fear of resistance to acyclovir. Why in these cases acyclovir was able to prevent recurrence in the allograft but not extrahepatic disease is unclear. Development of acyclovir resistance has been reported during prolonged post-LT acyclovir therapy [10]. In that case, sequencing of the HSV strain recovered from the allograft showed a base insertion in the thymidine kinase gene resulting in acyclovir resistance not present in the initial strain. Unfortunately, plasma DNA determinations before and after the recurrence of herpes infection were not performed. Because we feared breakthrough viraemia due to the development of acyclovir resistance, we continued to monitor viral DNA levels until the patient's death. Based on our experience, serial HSV DNA load determinations might be as a useful tool for post-LT monitoring of antiviral treatment and surveillance for breakthrough viraemia. Interestingly, HSV liver infections in immunocompromised patients are not always aggressive: transient liver enzyme elevations without compromised liver function have been reported in isolated cases [20]. In such situations, once other more frequent causes of liver tests alteration have been ruled out and in the absence of positive serology, determinations of plasma HSV DNAemia could also be considered to establish the diagnosis.

To conclude, our case illustrates the potential utility of plasma HSV DNA load determinations for diagnosis and monitoring therapy for HSV hepatitis, particularly following LT. Considering the serious prognosis of this disease, samples should be rapidly sent to the laboratory and empiric antiviral treatment initiated whenever herpetic hepatitis is suspected. Prospective studies will be required to determine factors influencing the outcome of liver transplantation for herpetic hepatitis and should help to select patient with a better post-transplant prognosis.

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Disclosure statement
The authors declare no competing interests.

References