Let's not forget herpes simplex virus in case of fulminant hepatic failure

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Abstract

Fulminant herpes simplex virus (HSV) hepatitis is a rare condition, which is usually identified only after orthotopic liver transplantation (OLT) or at autopsy. The most commonly affected individuals are immunosuppressed patients, although HSV hepatitis can occur in immunocompetent patients as well. A high degree of suspicion combined with early diagnostic modalities may improve survival. We present a case report of fulminant herpetic hepatitis, requiring OLT. In addition, a review of the literature was performed. (Acta gastroenterol. belg., **2014**, 77, **359-361**).

Key words : fulminant hepatic failure, herpes simplex virus, liver transplantation.

Introduction

Only 1.4% of all cases of fulminant hepatic failure (FHF) are related to herpes simplex virus (HSV). Most cases (58%) were diagnosed at autopsy (1,2). It has to be kept in mind that immunosuppressed patients and pregnant women are a high-risk population. In case of fulminant hepatitis, the differential diagnosis should include HSV, besides other viral and non-viral etiologies. Overall outcome is known to be poor so rapid intervention is mandatory to improve prognosis.

We present a case of FHF secondary to HSV, requiring orthotopic liver transplantation (OLT). In addition, a review of previously reported cases was performed.

Case report

A case of a 37-year-old male with FHF due to HSV is reported.

Initially, the patient was admitted with dysuria and persisting fever despite of a 7-day-ciprofloxacin coverage. There was no relevant medical history besides chronic use of methylprednisolone 20 mg for cluster headache .

On admission, leukocyturia was present but urine culture remained negative. Clinical examination, including external genital inspection, was normal. Temocillin was initiated empirically.

The patient developed thrombocytopenia and elevated liver enzymes. After three days, clinical deterioration followed with development of FHF (with Alanine Transaminase (ALT) up to 13980 U/l, Aspartate Transaminase (AST) 14450 U/l and International Normalized Ratio (INR) 2.1). Total and direct bilirubine were 3.3 and 3.0 mg/dl, respectively. Serological screening for viral infections was negative for Hepatitis B surface Antigen (HBsAg), Hepatitis C Virus Antibody (HCV Ab), Hepatitis A Virus Immunoglobulin M (HAV IgM), Epstein-Barr Virus (EBV) IgM and Cytomegalovirus (CMV) IgM and IgG. HCV RNA, HBV DNA, EBV DNA, CMV DNA and Varicella Zoster Virus (VZV) DNA were undetectable. Real-time PCR on blood revealed more than 10^9 copies/ml of HSV-2 DNA (3). HSV IgM was negative and IgG positive. Other causes of fulminant hepatitis were excluded and acyclovir was initiated.

Because of high-grade encephalopathy and a factor V level of 14%, the patient matched the Clichy criteria (4) and was put on the high urgency list for OLT.

The Clichy criteria include the presence of coma or confusion (equating to encephalopathy grades III-IV) as well as a factor V level, a non-vitamin K-dependent clotting factor, of less than 30% if over 30 years of age. He was transplanted four days after the initial diagnosis. Explant liver histopathology showed massive confluent necrosis with acute inflammation. Despite the absence of typical nuclear inclusion bodies and a negative immunohistochemic staining, this image was compatible with HSV infection. The graft appeared HBcAb and CMV IgG positive. Lamivudine and ganciclovir were added, respectively. Anti-hepatitis B immunoglobulins were given post OLT. The patient became anuric, requiring dialysis intermittently during two weeks. Two weeks after OLT, the patient developed critical illness polyneuropathy. Amitryptilin was initiated and the patient was enrolled in a revalidation program.

The liver function improved one and a half months after transplantation (Fig. 1). HSV DNA levels remained undetectable during follow-up. The patient was discharged two months after transplantation. His condition remains stable under tacrolimus and mycophenolic acid as standard immunosuppression therapy, along with lamivudine and acyclovir as life-long antiviral prophylaxis. Ganciclovir was stopped after two months, due to neutropenia.

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Discussion

FHF is a rare complication of HSV infection, and has been most frequently reported in immunocompromised hosts. This risk group includes pregnant women in their third trimester (lower T cell count), as illustrated by the first reported case in 1969 (5). HSV hepatitis can occur in immunocompetent patients as well. Without pre-existing liver-cirrhosis and a duration of illness less than twenty-six weeks, the combination of coagulopathy (INR ≥ 1.5) and encephalopathy defines FHF (6).

HSV comprises less than 1% of all cases of FHF and accounts for less than 2% of the viral etiologies (7). Both HSV types can induce FHF, although HSV type 2 is more frequent, probably because HSV-2 primary infections are more common in adulthood as sexually transmitted diseases (1). Four mechanisms of HSV dissemination and hepatitis in immunocompetent hosts have been proposed : a large HSV inoculum at the time of initial infection, an occult impairment in cellular immunity (i.e. occult defects in the T lymphocytes and/or macrophages to respond or process the HSV antigen), reactivation of a latent virus in association with reinfection by a second strain of HSV, or infection with a hepatovirulent strain (8). The presentation is typically that of an anicteric hepatitis with AST levels higher than ALT levels (9). On clinical examination, herpetic lesions are usually absent. Serological assays have limited value for establishing an early diagnosis.

Diagnostic PCR methods providing rapid results should be implemented and liver biopsy considered (1). Because of increased bleeding risk, the transjugular route is preferred when taking biopsies. Cowdry type A inclusion bodies are typically present. These are purple nuclear inclusions with a clear halo in the hepatocytes. Immunohistochemic staining can be used to detect viral antigen. Both findings were absent in our patient, presumably because of massive liver necrosis.

The spontaneous prognosis of HSV-related hepatitis is poor. This could be related to late suspicion of this specific illness and consequently, delayed treatment. The mortality rate reaches almost 90% (2), while the five year survival rate after OLT is 38% (10). After exclusion of common causes of fulminant hepatitis, systemic preemptive treatment with acyclovir should be started (1,2). This treatment could be stopped when viremia or histology turns out to be negative. A significantly lower rate of progression to OLT or death in acyclovir-treated patients compared to untreated, has been shown.

Lifelong antiviral therapy after OLT is likely required to prevent recurrences (11). However, point mutations in the viral thymidine kinase or the viral DNA polymerase may result in failure to stop viral replication, despite appropriate therapeutic schemes ; because the mutations possibly confer resistance to several antiviral drugs (12). The emergence of resistant strains that cause significant disease unresponsive to antiviral drugs has been reported in patients with hematological malignancy, transplant

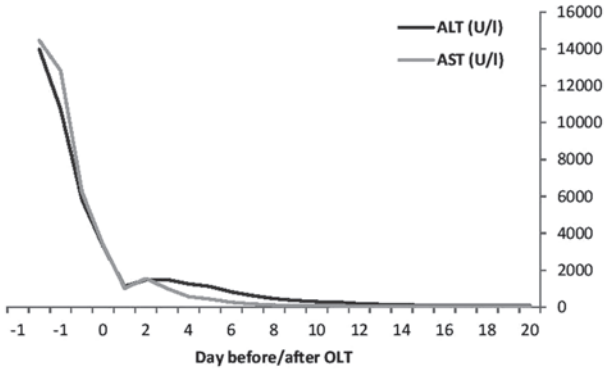

Fig. 1. — Evolution of serum transaminase levels after orthotopic liver transplantation. The pre-operative dip in liver enzymes could be explained by exhaustion of the hepatocytes.

recipients and other immunocompromised patients. Careful monitoring of these patients is necessary, and complementary resistance testing should be performed when disease seems unresponsive to antiviral therapy. In the case of therapeutic failure of acyclovir, foscarnet could be an alternative. And when additionally resistance to foscarnet appears, cidofovir remains as a therapeutic option (13).

In determining the likelihood of clinical progression, prognostic markers on presentation and during the course of disease would be of great use. A retrospective analysis learned that common features on presentation included fever, high aminotransferases, leukopenia, thrombocytopenia, encephalopathy, coagulopathy and acute renal failure. Older age (> 40 years), male gender, immunocompromised state, the degree of aminotransferase elevation (ALT > 5000 U/l), the absence of antiviral therapy, platelet count < 75000/l and the presence of coagulopathy and encephalopathy were significantly associated with progression of disease. These predictors of outcome emphasize the need for early treatment and immediate OLT evaluation to increase survival (2). Note that our patient met six out of the eight negative prognostic markers. Fortunately, he received early antiviral therapy. OLT couldn't be avoided and was performed four days after the initial diagnosis.

Several published cases, including our patient's, showed a significant reduction of viral load post-OLT (14). This suggests that the removal of the infected liver, as a major reservoir for HSV, might be effective in reducing the viral load. However, post-OLT extrahepatic HSV disease during acyclovir treatment, and despite undetectable viraemia, has been described (14). Serial HSV DNA load determinations might be useful for post-OLT monitoring of antiviral treatment (15). Prospective studies will be required to determine factors influencing the outcome of OLT for herpes-related hepatitis and should help to select patients with a better post-OLT prognosis, but due to the rarity of the condition it seems unlikely to

be realistic. For now, OLT in adults should probably be considered only for selected patients in otherwise good general health (9). As illustrated in our case report, OLT can be performed successfully in select patients. It is obvious that frequent follow-up remains necessary.

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