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Case report

Herpes simplex hepatitis after liver transplantation: case report and literature review

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Abstract: Herpes simplex virus (HSV) hepatitis is an uncommon cause of liver failure, but may have a dramatic outcome. We herein present a case report of a liver graft infection by HSV-1 associated with liver failure and encephalitis. A complete hospital chart review of the case and a literature search were undertaken. Literature review suggests that herpes simplex acute liver failure is rare and associated with a poor prognosis, even with early treatment. Novel diagnostic and preventive approaches need to be instituted.

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Herpes simplex hepatitis is an uncommon cause of liver failure but may have a dramatic outcome. A case report of a liver graft infection by herpes simplex virus-1 (HSV-1) associated with liver failure and encephalitis is presented. A complete hospital chart review of the case and a literature search were undertaken. Literature review suggests that herpes simplex acute liver failure is rare and associated with a poor prognosis, even with early treatment. A high index of suspicion is warranted, and novel diagnostic and preventive approaches need to be instituted.

Case report

A 64-year-old male patient underwent liver transplantation for non-alcoholic steato-hepatitis cirrhosis. At the time of surgery, his model for end-stage liver disease score was 19. Preoperative serology for human immunodeficiency virus, hepatitis B virus, and hepatitis C virus were negative. The patient had never had any clinical manifestation of herpes simplex before transplantation. His past medical history was noteworthy for hypertension, dyslipidemia, and hypothyroidism.

The donor was a 22-year-old man who died from a gunshot trauma. His past medical history was unremarkable and no clinical manifestation of herpes simplex was noted.

Liver transplantation was performed using a classic end-to-end cavo-caval anastomosis. The cold ischemia time was 16 h and operative blood loss was 1 L. The patient did not receive any blood products during the surgery or in the immediate postoperative period. Standard cefazolin prophylaxis was administered.

Both the donor and the recipient had negative cytomegalovirus (CMV) serologies, precluding any need for antiviral prophylaxis, based on the CMV guidelines. Immunosuppression was induced with methylprednisolone, tacrolimus, and azathioprine. The patient developed postoperative renal failure associated with calcineurin inhibitors. Tacrolimus was temporarily withheld, and basiliximab was administered on postoperative day (POD) 1 and POD 4, and tacrolimus reintroduced after improvement of renal function.

On POD 9, the patient complained of abdominal pain associated with a body temperature of 39.2°C. Blood tests showed a normal white blood cell (WBC) count of 5.8×10^9/L and slightly elevated liver enzymes (Table 1). A Doppler ultrasound showed normal vascular flows and a normal biliary tract. An abdominal computed tomography (CT) scan was performed and was unremarkable. After a negative infectious workup, empiric therapy with intravenous (IV) piperacillin-tazobactam and vancomycin was instituted. Herpesviridae serology was negative for CMV, HSV-1, and HSV-2.

Two days later (POD 11), liver function tests were consistent with a worsening cytolytic pattern associated with a significant leukopenia and lymphopenia (WBC: 3.6×10^9/L, lymphocytes: 0.1×10^9/L) and some circulatory dysfunction (Table 1). A liver biopsy was then performed. Microscopic evaluation and immunochemistry studies rapidly suggested HSV hepatitis. IV acyclovir (10 mg/kg IV every 8 h) was started. Two days later, the viral culture performed on the liver biopsy specimen came back positive for HSV-1.

On POD 13, the patient continued to deteriorate and developed progressive encephalopathy without focal neurological symptoms. Liver function tests suggested severe acute hepatitis associated with progressive liver failure (Table 1). The patient did not present any hypoglycemia, and both the brain CT scan and the magnetic resonance imaging (MRI) were normal at that time. An electroencephalogram showed absence of focal irritability. The patient was transferred to the intensive care unit 2 days later because of worsening encephalopathy requiring endotracheal intubation. Even if his neurological dysfunction was considered related to the ongoing liver failure, his general clinical state precluded a second liver transplantation.

Patient blood test results by postoperative day (POD)

Test	POD 9	POD 11	POD 13	POD 15
AST (U/L)	37	567	8728	3690
ALT (U/L)	53	562	5400	2710
Bilirubin (μmol/L)	20	17	19	23
Alk-phos (U/L)	44	40	88	125
WBC ($\times 10^9$/L)	7.6	3.1	2.8	1.5
INR	1.1	1.3	2.3	2.1
PLT ($\times 10^9$/L)	59	86	75	55
Fibrinogen (g/L)	n/a	n/a	n/a	0.92

AST, aspartate aminotransferase; ALT, alanine aminotransferase; Alk-phos, alkaline phosphatase; WBC, white blood cell count; INR, international normalized ratio; PLT, platelet count; n/a, not available.

Table 1

On the following days in the intensive care unit, the patient's liver function improved, although the encephalopathy did not. A cerebrospinal fluid examination was performed 2 weeks after acyclovir had been started and was positive for HSV (non-specific in-house real-time polymerase chain reaction [PCR] assay). Same-day serum PCR was also positive for HSV-1 (specific in-house PCR assay). Although acyclovir was still administered at an optimal dosage, the patient's neurologic condition further deteriorated. He progressively developed circulatory failure, renal failure, and disseminate intravascular coagulation.

Microbiological and imaging studies were compatible with probable pulmonary angioinvasive aspergillosis (immunosuppressed patient, positive sputum for galactomannan antigen assay, positive sputum culture for *Aspergillus fumigatus*, multinodular perivascular infiltrates on pulmonary scan) (1). A brain MRI showed multinodular hyperdensities suggesting abscesses caused by cerebral aspergillosis dissemination. An abdominal CT scan also showed multiple hypodensities in the spleen, suggesting splenic involvement as well. IV voriconazole was then introduced. Another serum PCR assay for HSV, performed 2 weeks after the positive one, came back negative. Treatments were continued for another week, but the patient's general clinical state deteriorated. Supportive therapies were withdrawn after family consent and the patient died 1 month after liver transplantation.

Later on, we retrospectively tested the donor's serum, and the test came back positive for HSV-1 (non-specific in-house PCR assay), suggesting that our patient could have acquired the disease from the donor.

Discussion

This case shows a fulminant and dramatic course of HSV-1 acute infection in a seronegative liver transplant (LT) recipient. Although appropriate therapy was instituted rapidly, the patient died from multiorgan failure associated with disseminated angioinvasive

aspergillosis, a well described complication of cellular immunosuppression and liver failure (1, 2).

Careful attention is paid to the Herpesviridae family in pre-transplant evaluations (3–5). Indeed, CMV serology is systematically performed in every donor and recipient. Prophylactic ganciclovir or valganciclovir (or preemptive approach based on CMV viral load screening) has been recommended in the first 3–6 months after transplantation in patients with different combination of positive CMV serology (4). Such prophylaxis also covers other infections from the Herpesviridae family, such as HSV-1, HSV-2, and varicella zoster virus. In many centers such as ours, no systematic screening or prophylaxis is done for Herpesviridae viruses other than CMV (3).

HSV-1 or -2 hepatitis is a rare but very serious disease. It has been reported only in small case series or case reports (6). HSV infection seems to mainly affect children, pregnant women, and patients whose immunity is compromised (7), including solid organ recipients such a LT recipients (8). In infected patients, evolution to acute liver dysfunction is common and rapid. Sometimes, liver transplantation had to be performed (9). The diagnosis is often delayed or missed because of its non-specific clinical presentation. Hence, a significant proportion of the first cases described were solely diagnosed at autopsy (9, 10). It is only since the late 1980s that herpes simplex hepatitis has been described in LT recipients (8, 11).

We performed a literature review through a PubMed search using the terms "liver transplantation," "herpes simplex," "acute liver failure," and "hepatitis," and kept only the articles about HSV hepatitis in LT recipients. Our literature search yielded 19 cases that met our criteria. However, our review probably underestimates the real incidence of the disease, because of non-reported and non-diagnosed cases. Table 2 summarizes the reported cases that we found (6, 8, 11–17), and our own.

In LT recipients, herpes simplex hepatitis seems to occur very early in the postoperative course. Available data suggest that the timing of presentation is 20 ± 12 days post transplant on average, if Case 11 (Table 2) is excluded. This patient was excluded because the herpes hepatitis appeared in the course of a Crohn's disease exacerbation treated with some extra immunosuppressive drugs (12). In comparison, CMV hepatitis in LT patients usually occurs >1 month after transplantation (4, 17). The real interval between transplantation and onset of herpes hepatitis might even be shorter than that reported, as some cases were only diagnosed at autopsy. The short interval between transplantation and acute hepatitis might suggest reactivation of the virus in the recipient because of immunosuppressive drugs or donor-acquired primary infection, rather than a community-acquired primary infection. As already mentioned, systematic screening for HSV serology in donors and recipients is not routinely performed in every center, including ours.

Diagnosis is difficult because of the low prevalence and the non-specificity of the clinical presentation. According to the literature, fever, highly abnormal liver function test results without jaundice, right superior quadrant abdominal pain, and leukopenia are the signs and symptoms most often reported (6, 18). Mucocutaneous lesions seem to be present in only 27% of a general population suffering from herpes hepatitis (10) compared with 31% in LT patients (Table 2). This clinical presentation could therefore be mistaken for acute rejection or graft vascular compromise.

Moreover, evidence suggests that early initiation of empirical antiviral treatment with IV acyclovir significantly improves survival (6, 8, 10, 17), especially in children. In LT patients, the global high mortality rate of 58% and the dichotomous outcome based on presence or absence of treatment in our review (100% mortality in untreated patients [$n = 6$] and 38% in treated patients [$n = 14$]; Table 2) suggest the importance of early diagnosis and treatment.

Because early detection and diagnosis seem essential to improve survival (6, 9, 10), a high index of suspicion is warranted in the first month after liver transplantation. Patients with acute hepatitis associated with leukopenia, right upper quadrant pain, and fever should be investigated for herpes hepatitis. Both HSV PCR and liver biopsy should be performed to establish the diagnosis and to exclude an alternative diagnosis, such as acute rejection (5). Once the diagnosis is suspected, treatment with acyclovir should be empirically initiated as soon as possible (5, 15). One of the cases found from our search (Case 13) developed HSV hepatitis, although prophylaxis had been given. This patient survived, suggesting that prophylaxis might be associated with a better outcome even if clinical hepatitis occurs.

Because the outcome of such a clinical disease is devastating, prevention is warranted. Specific prophylaxis for HSV has been associated with a reduced incidence of clinical disease and has been recommended in recent guidelines for HSV-seropositive solid organ recipients not receiving CMV prophylaxis (5). However, authors of those guidelines could not recommend a clear prophylactic approach for HSV-seronegative recipients not receiving CMV prophylaxis, mostly owing to a lack of data. Moreover, the impact of the donor HSV serologic status was not taken into account

Cases of herpes simplex hepatitis after liver transplantation

Author (reference)	Case no.	Age in years	Gender	No. days after transplant diagnosed	Diagnosed by Biopsy (B) or Autopsy (A)	Primary (P) or Reactivation (R)	Other site(s)	Acyclovir therapy	Outcome: Died (D) or Survived (S)
Present report	1	64	M	10	B	P	Cerebral	At diagnosis	D
Ichai et al. (6)	2	48	F	31	A	P	None	None	D
Kusne et al. (8) – 8 cases	3	26	F	18	A	R	Lung, larynx, trachea, bladder	None	D
	4	36	M	21	B	R	Thigh	4 weeks before death	D
	5	42	F	46	A	R	Throat, urine	None	D
	6	51	F	25	A	R	Lung, larynx, trachea, esophagus, stomach, adrenal	None	D
	7	24	F	30	B	R	n/a	At diagnosis	S
	8	26	F	5	B	R	n/a	At diagnosis	S
	9	54	F	14	B	P	Throat, thigh	At diagnosis	S
	10	29	F	6	B	R	n/a	At diagnosis	S
Bissig et al. (12)	11	40	n/a	1440	B	P	Genital, skin	At diagnosis	S
Longerich et al. (13)	12	61	M	8	B	P	n/a	At diagnosis	D
Hori et al. (14)	13	4	F	8	B	R	None	Prophylaxis and at diagnosis	S
Basse et al. (15) – 2 cases	14	35	M	19	B	n/a	Skin	At diagnosis	S
	15	58	M	12	B	P	Skin	At diagnosis	S
Singh et al. (11) – 3 cases	16	n/a	n/a	21	A	R	None	None	D
	17	n/a	n/a	46	A	R	Lung, colon, larynx	None	D
	18	n/a	n/a	21	B	P	Lung	At diagnosis	S
Nebbia et al. (16)	19	44	F	15	B	P	Adrenal, spleen, adenopathy	At diagnosis	D
Campsen et al. (17)	20	57	F	22	B	P	None	At diagnosis	D

no., number; M, male; F, female; n/a, not available.

Table 2

in these guidelines (5). Our HSV-seronegative patient received a graft from an HSV-1–seropositive donor and had no indication for CMV prophylaxis. In this case, a clinical monitoring was probably indicated and some antiviral prophylaxis could have been justified based on the donor serologic status, an approach similar to that recommended for CMV (4). However, the donor information was unknown at that time, because our Organ Procurement Organization does not perform systematic screening for HSV, and such an approach for HSV has never been recommended in the literature.

Given the high mortality associated with acute HSV hepatitis in LT patients and the available data, a high index of suspicion and a low trigger to start early empiric treatment are warranted to improve outcome. Because of the life-threatening nature of the disease, pre-transplantation systematic serologic screening for HSV in donors and recipients should be universal, and antiviral prophylaxis probably more liberal. This case suggests that clinical monitoring or antiviral prophylaxis should be considered in HSV-seronegative solid organ recipients not receiving CMV prophylaxis, with special attention if matched with a seropositive donor. However, more data are warranted to better evaluate benefits of prophylaxis in different serologic status subgroups of solid organ recipients, especially in seronegative patients, and the associated impact of the donor serologic status for the latter. The optimal duration of both prophylaxis and treatment of an acute episode of hepatitis should also be evaluated further.

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