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TRANSPLANT INFECTIOUS DISEASE

BRIEF COMMUNICATION

Donor-derived fulminant herpes simplex virus hepatitis after liver transplantation: Two cases and review of literature

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*see Appendix 1

Abstract

Background: Fulminant herpetic hepatitis due to herpes simplex virus (HSV), serotype 1 or 2, is a rare but often fatal complication after solid organ transplantation (SOT). HSV hepatitis in SOT recipients can occur either due to primary infection acquired post transplantation, viral reactivation in a seropositive patient, or as donor-derived infection. Cases of fatal hepatitis have been reported in the liver as well as in other SOT recipients. The fatal outcome is mostly due to delayed diagnosis and treatment, which is explained by the lack of clinical specificity of HSV hepatitis.

Methods: We report two cases of fatal donor-derived HSV hepatitis in liver-transplanted recipients. We reviewed all published cases of donor-derived HSV infections after SOT with an evaluation of the presence of prophylaxis and outcome.

Results: In both liver recipients, the retrospective determination of HSV serostatus was negative, and both cases occurred in the absence of cytomegalovirus or HSV prophylaxis. A review of the literature showed a significant series of cases of severe

Abbreviations: ALF, acute liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CMV, cytomegalovirus; CRP, C-reactive protein; CT, computed tomography; Ct, PCR cycle threshold; D, donor serostatus; GFR, glomerular filtration rate; HSV, herpes simplex virus; IHC, immunohistochemistry; LT, liver transplantation; PCR, polymerase chain reaction; POD, post-operative day; PT, prothrombin time; R, recipient serostatus; SOT, solid organ transplantation.; STCS, Swiss Transplant Cohort Study

Ilana Reinhold and Laurent Teasca contributed equally to this study.

hepatitis, mostly fatal, as well as the absence of specific preventive therapy guidelines in cases of HSV serology mismatch.

Conclusions: The occurrence of two fatal donor-derived hepatitis made the Swiss Transplant Infectious Diseases working group modify its national recommendations regarding pretransplant serostatus determination and HSV prophylaxis after liver transplantation. Further studies are needed to assess this approach.

KEYWORDS
donor-derived infection, guidelines, herpes simplex virus, liver transplantation

1 | INTRODUCTION

Herpes simplex virus (HSV) hepatitis is a rare complication of HSV infection often leading to acute liver failure (ALF) with potentially fatal outcome. It occurs most frequently in solid organ transplant recipients and children and during pregnancies.[1] Either triggered by a primary infection or by reactivation, febrile hepatitis often presents without mucocutaneous lesions. Donor-derived HSV hepatitis after liver transplantation (LT) has been rarely documented.[2] Here, we report two cases of fatal "proven" donor-derived HSV fulminant hepatitis after LT with implications for the Swiss national prophylaxis recommendations.

2 | METHODS

The two fatal cases prompted a review of the local protocols. A review of the literature regarding all published cases of donor-derived HSV infections after solid organ transplantation (SOT) was performed. Cases were analyzed concerning HSV serostatus of donor and recipient, HSV prophylaxis, and outcome.

3 | RESULTS

3.1 | Case 1

A 58-year-old female underwent a second LT due to recurrent primary sclerosing cholangitis from a 64-year-old female donor. Both the recipient and donor cytomegalovirus (CMV) serostatus were positive (donor serostatus [D]+/recipient serostatus [R]+). HSV serostatus of the recipient was negative and unknown at the time of transplantation for the donor. Immunosuppression consisted of methylprednisolone and tacrolimus. On post-operative day (POD) 1, meropenem was initiated for *Enterobacter cloacae* bacteremia, vancomycin for *Enterococcus faecium* in the drain fluid and fluconazole. On POD 8, she developed abdominal pain and hypotension. Laboratory investigation showed increasing liver enzyme values (aspartate aminotransferase [AST] from 197 to 6600 U/L and alanine aminotransferase [ALT] from 307 to 2194 U/L), and a C-reactive protein (CRP) rising from 29 to 98 mg/L. Factor V dropped from 114% to 15 % and prothrombin time (PT) was 17.3 s. A computed tomography (CT) scan excluded vascular thrombosis and bleeding. Explorative laparotomy showed serous ascites and a stiff liver aspect. Relapse of primary sclerosing cholangitis or organ rejection was suspected, and mycophenolate mofetil was added and methylprednisolone increased. A super-urgent liver re-re-transplantation was performed on POD 11 from an 89-year-old brain-dead female donor. CMV viremia was 1505 IE/mL, and ganciclovir was initiated on POD 13. Pathological examination of the explanted liver revealed hemorrhagic liver necrosis and hepatocyte nuclei alterations compatible with HSV, confirmed by immunohistochemistry (IHC; Figure 1A). Disseminated donor-derived HSV infection was suspected, and ganciclovir was replaced by acyclovir (10 mg/kg every 8 h) on POD 13 and immunosuppression stopped. A retrospective HSV-2 polymerase chain reaction (PCR) of the first donor showed a viremia of 147 copies/mL. Retrospective measurements of HSV-2 viremia of the recipient on POD 9 showed a PCR cycle threshold value (Ct) of 15.9 and a Ct value of 17.8 on POD 14 confirming disseminated HSV-2 infection. Intravenous immunoglobulin and plasmapheresis were provided as additional therapies. Due to rapidly progressing severe multi-organ failure, therapeutic withdrawal was decided on POD 14 (1 day after the initiation of acyclovir). An autopsy revealed multiple perforations of the esophagus and stomach and focal liver necrosis, all positive for HSV in IHC, including the biopsy of the second liver transplant (Figure 1B).

3.2 | Case 2

A 66-year-old male patient with alcoholic cirrhosis, complicated by hepatocellular carcinoma, underwent LT from a 75-year-old female donor. Induction immunosuppression consisted of basiliximab, followed by tacrolimus, mycophenolate mofetil, and methylprednisolone. CMV serology constellation was D+/R+, and a preemptive follow-up was initiated. On POD 6, the patient became febrile, and CRP increased from 10 to 50 mg/L. Piperacillin-tazobactam and caspofungin were started. A CT scan showed moderate intra-abdominal liquid and two segmentary pleural embolisms. Therapeutic anticoagulation was initiated. The patient remained febrile, and liver enzymes started to increase on POD 9, with AST at 470 U/L and ALT at 170 U/L, PT dropping to 52% and a reduction of glomerular filtration rate (GFR) to 35 mL/min/1.73m^2. On POD 11, the patient developed severe

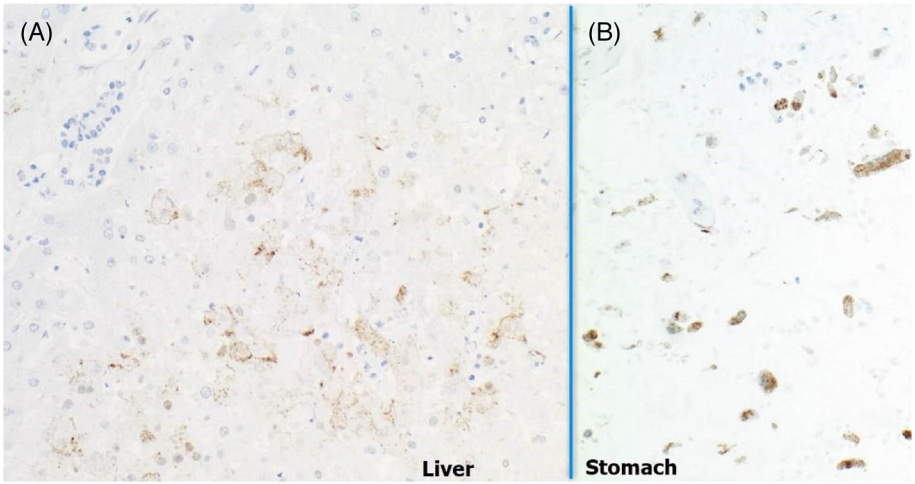

FIGURE 1 Case 1. Herpes simplex virus (HSV) immunostaining (brown) in the liver (A) and stomach (B) (see nuclear moulding, upper right).

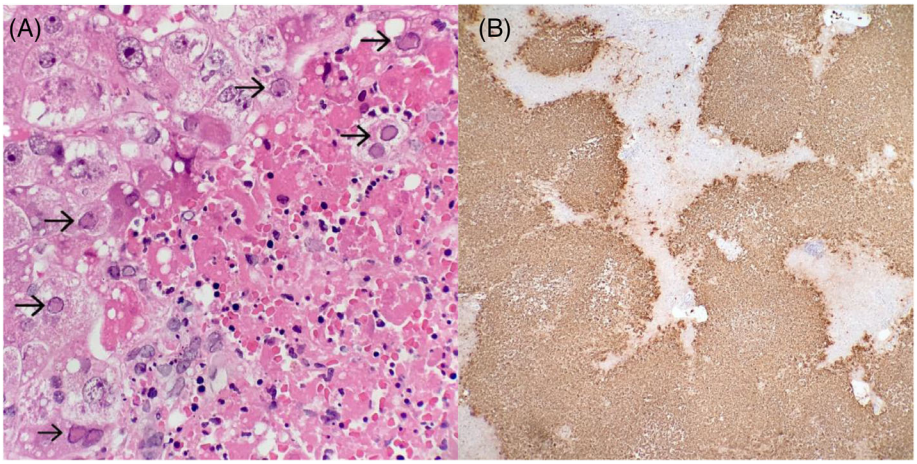

FIGURE 2 Case 2. High power view of hematoxylin–eosin staining (A) of the liver biopsy showing intranuclear inclusion bodies that peripheralize nuclear chromatin (black arrows) sometimes within bi-nucleate hepatocytes. HSV immunostaining (B) of the liver biopsy.

lactic acidosis. Laboratory investigation showed a PT of 26%, a factor V of 15%, further elevation of transaminases with AST 6000 U/L, ALT 1200 U/L, thrombocytes of 45 G/L, and a further decline in GFR to 16 mL/min/1.73m^2. An emergency laparotomy showed a small, yellowish liver, and non-purulent ascites. Because of uncontrolled hemorrhage with multi-organ failure, therapeutic withdrawal was decided. An autopsy revealed histopathological signs of HSV hepatitis with viral nuclear inclusions, extensive necrosis (Figure 2A), and a positive HSV-1 IHC (Figure 2B) without extrahepatic sites of HSV infection. Retrospectively, the HSV serology constellation was D+/R−. An initially (POD 1) negative ultrasensitive HSV-1 blood PCR became detectable with a Ct value of 29 on POD 7 and 15 on POD 11, demonstrating rapidly increasing viremia. The donor's serum tested negative for HSV DNA.

3.3 | Literature review

A literature review found 14 reports with over 50 cases, of which 20 cases (kidney [$N = 8$] and liver [$N = 7$] recipients) were sufficiently documented (Table 1). All except one occurred in the early post-transplant period in the absence of HSV prophylaxis (mean time 14 days post transplant), one case occurred several months post transplantation after stopping HSV prophylaxis. Mortality reached 71% in liver recipients. Four patients developed HSV hepatitis despite positive HSV pre-transplant serologies. For two seropositive patients, the hepatitis was due to the HSV virus of the other genogroup.

4 | DISCUSSION

We describe two cases of fatal HSV hepatitis after LT matching the definitions of "proven" donor-derived HSV infections.[3] Potential HSV donor-derived infections have been described in lung, liver, and kidney transplant recipients.[4] The disease typically occurs in the very early post-transplant period at the time of most intense immunosuppression due to induction therapy.[5] The short interval between LT and disease suggests that viral reactivations or primary donor-derived infections are more likely than community-acquired primary infections.

TABLE 1 Published cases of donor-derived herpes simplex virus (HSV) 1 or 2 infections after solid organ transplantation.

Author, year of publication	Age, gender	Type of transplant	Donor HSV serology profile	Receptor HSV serology profile	HSV prophylaxis	Time of onset of symptoms following transplant	Diagnosis (PCR, blood)	Outcome
Koneru, 1998	21, M	Kidney	HSV 1/2 positive	HSV 1/2 negative	No	10 days	HSV 2 positive	Died
	30, M	Kidney	HSV 1/2 positive	HSV 1/2 negative	No	10 days	HSV 2 positive	Died
Gabel, 1988	48, M	Kidney		HSV 1/2 negative	No	21 days	HSV 1 positive	Survived
Goodman, 1989	30, F	Pancreas	HSV 1/2 positive	HSV 1/2 negative	No	8 days	HSV 2 positive	Died
	64, F	Heart	HSV 1/2 positive	HSV 1/2 negative	No	14 days	HSV 2 positive	Survived
Kusne, 1991	26, F	Liver	HSV 1/2 positive	HSV 1 negative HSV 2 positive	No	18 days	HSV 1 positive	Died
Nebbia, 2006	44, F	Liver	HSV 1 negative HSV 2 positive	HSV 1/2 negative	No	10 days	HSV 2 positive	Died
Basse, 2008	58, M	Liver	ND	HSV 1/2 negative	ND	12 days	HSV 2 positive	Survived
Al Midani, 2011	26, F	Kidney	HSV 1 positive HSV 2 negative	HSV 1/2 negative	No	14 days	HSV 1 positive	Survived
	59, M	Kidney	HSV 1/2 negative	HSV 1/2 negative	No	12 days	HSV 1 positive	Died
Côté D, 2014	64, M	Liver	HSV 1 positive HSV 2 negative	HSV 1/2 negative	No	9 days	HSV 1 positive	Died
Pietrucha-Dilanchian, 2016	24, F	Heart	ND	HSV 1/2 positive	No	3 years	HSV 2 positive	Died
Feugeas, 2016	41, F	Kidney–Pancreas	HSV 1/2 negative	HSV 1/2 negative	No	23 days	HSV 1 positive	Survived
Macesic, 2017	30, M	Kidney–Pancreas	HSV 1 negative HSV 2 positive	HSV 1/2 negative	No	7 days	HSV 2 positive	Died
	20, F	Liver	HSV 1 negative HSV 2 positive	HSV 1/2 positive	No	13 days	HSV 2 positive	Survived
Shaw, 2018	31, F	Kidney	HSV 1 negative HSV 2 positive	HSV 1/2 serology negative	6 months val-ganciclovir	7 months	HSV 2 positive	Survived
Zeidan, 2021	43, F	Kidney	HSV 1 negative HSV 2 positive	HSV 1 positive HSV 2 negative	No	9 days	HSV 2 positive	Survived
Arana, 2022	66, F	Liver	ND	HSV 1/2 negative	No	14 days	HSV 1 positive	Died
	69, M	Liver	ND	HSV 1/2 negative	No	13 days	HSV 1 positive	Died
	45, F	Kidney	ND	HSV 1/2 negative	No	21 days	HSV 1 positive	Died

The clinical presentation of our cases was non-specific as previously described,[1,6] with a large differential diagnosis delaying diagnosis and start of therapy. Diagnosis of HSV hepatitis was finally made in both cases by pathology, which remains the gold standard.[11]

Both patients had an intermediate risk CMV donor-recipient constellation and were followed preemptively according to local guidelines. Both recipients had negative HSV serologies, with the donor HSV serologies unknown at the time of transplantation. A positive HSV viremia was detected retrospectively in the donor of the first case. The short delay between transplant and disease, the negative recipient's serostatus, combined with the HSV-positive donor serologies led us to assume that both cases fulfill the definition for "proven" donor-derived disease transmission.[3]

High-dose intravenous acyclovir and LT are suggested as treatments for fulminant HSV hepatitis in other settings.[6,7] To our knowledge, there is only one report of re-transplantation for post-liver transplant fulminant HSV hepatitis.[8]

Early plasmapheresis was associated with an improvement of transplant-free survival in patients with ALF.[9–11] The benefit of plasmapheresis in ALF due to HSV hepatitis remains unknown but has been successfully used in two cases.[12,13] Prophylactic ganciclovir or valganciclovir provided against CMV also efficiently prevents HSV infection, reducing the risk of HSV reactivation at 1-year post transplant from 9.8% to 3% for all clinical presentations including both mucocutaneous and non-mucocutaneous forms.[14] Of notice, only one of the 20 cases described in Table 1 had received valganciclovir

prophylaxis, stopped one month before the patient developed HSV hepatitis.

Current guidelines recommend considering HSV prophylaxis in seropositive recipients without CMV prophylaxis.[7] However, there is no specific recommendation for HSV prophylaxis in adult patients in case of a D+/R− constellation.[7] Due to the high prevalence of HSV seropositivity, specific anti-HSV prophylaxis was previously not routinely provided in Switzerland.[14] Following these two fatal cases in liver recipients and the lower risk expected for other organ transplants, the Swiss national recommendations were modified : (I) all liver donors and recipients should have a pre-transplant HSV serology, (II) in liver recipients with a CMV preemptive follow-up strategy and an unknown HSV serology, early valacyclovir prophylaxis starting 24 h following LT is recommended and continued in case of an HSV D+/R− constellation for 3–6 months depending on the intensity of the immunosuppression. Whether distinction between HSV1 or HSV2 should be made remains unclear as some cross-protection is expected between both genogroups.[15] Further surveillance studies will be required to assure the safety of this approach.

AUTHOR CONTRIBUTIONS

Writing original draft, *investigation*, *and visualization*: Ilana Reinhold and Laurent Teasca. *Conceptualization*, *design*, *writing original draft*, *and editing*: Christian van Delden. *Conceptualization*, *design*, *review*, *and editing*: Nicolas J Mueller. *Review and editing*: Matthias Hilty, Rea Andermatt, and Beat Müllhaupt. *Figure material*: Francesca Saro and Elena Requejo Rodriguez. *Resources*: Thierry Berney and Philipp Dutkowski.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1

The members of the Swiss Transplant Cohort Study (STCS) are: Patrizia Amico, John-David Aubert, Vanessa Banz, Beckmann Sonja, Guido Beldi, Christoph Berger, Isabelle Binet, Pierre-Yves Bochud, Sanda Branca, Heiner Bucher, Thierry Carrel, Emmanuelle Catana, Sabina

de Geest, Olivier de Rougemont, Michael Dickenmann, Joëlle Lynn Dreifuss, Michel Duchosal, Thomas Fehr, Alexander Leichtle, Christian Garzoni, Christophe Gaudet, Déla Golshayan, Jörg Halter, Dimitri Hauri, Dominik Heim, Christoph Hess, Sven Hillinger, Hans Hirsch, Patricia Hirt, Uyen Huynh-Do, Franz Immer, Michael Koller (head of the data center), Bettina Laesser, Brian Lang, Roger Lehmann, Oriol Manuel, Hans-Peter Marti, Michele Martinelli, Katell Mellac, Aurélia Merçay, Karin Mettler, Nicolas Mueller (chairman, Scientific Committee), Antonia Müller, Thomas Müller, Ulrike Müller-Arndt, Beat Müllhaupt, Mirjam Nägeli, Manuel Pascual (executive office), Klara Posfay-Barbe, Juliane Rick, Anne Rosselet, Simona Rossi, Silvia Rothlin, Frank Ruschitzka, Urs Schanz, Stefan Schaub, Aurelia Schnyder, Federico Simonetta, Katharina Staufer, Jürg Steiger (head, excecutive office), Guido Stirniman, Christian Toso, Christian Van Delden (executive office), Jean-Pierre Venetz, Jean Villard, Madeleine Wick (STCS coordinator), Markus Wilhlem, and Patrick Yerly.