Fatal systemic herpes simplex virus infection with atypical clinical manifestation early after living donor liver transplantation

Hye-Sung Jo¹, Pyoung-Jae Park², Wan-Joon Kim³, Hyung Joon Han⁴,
Young-Dong Yu¹, Dong-Sik Kim¹

¹Division of HBP Surgery and Liver Transplantation, Department of Surgery, Korea University Anam Hospital, Korea University College of Medicine, Seoul

²Division of Transplantation and Vascular Surgery, Department of Surgery, Korea University Guro Hospital, Korea University College of Medicine, Seoul

³Division of Hepatobiliary Pancreatic Surgery, Department of Surgery, Korea University Guro Hospital, Korea University College of Medicine, Seoul

⁴Division of Hepatobiliopancreas and Transplant Surgery, Korea University Ansan Hospital, Ansan, Korea

Received October 24, 2021

Revised November 15, 2021

Accepted November 17, 2021

Published online November 22, 2021

Corresponding author: Dong-Sik Kim
Division of HBP Surgery and Liver Transplantation, Department of Surgery, Korea University Anam Hospital, Korea University College of Medicine, 73 Goryedae-ro, Seongbuk-gu, Seoul 02841, Korea
E-mail: kimds1@korea.ac.kr
https://orcid.org/0000-0002-0608-1580

© The Korean Liver Transplantation Society

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Herpes simplex virus (HSV) infection in immunocompromised hosts after liver transplantation could cause visceral dissemination and fatal outcomes. Here, we report a fatal systemic HSV infection with atypical clinical presentation early after living donor liver transplantation. A 45-year-old female patient with chronic alcoholic liver cirrhosis underwent living donor liver transplantation using a left liver graft. The patient was clinically stable, and her liver function was recovering without any problems until postoperative day 12. However, mild erythematous erosive patches developed on both palms and soles. Although various topical steroids were applied and antihistamines were administered, the skin lesions gradually spread to the trunk and worsened with severe pain. Several days after the onset of skin lesions, aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels increased rapidly without specific findings on the CT scan. Therefore, we decided to perform skin and liver biopsies. The patient rapidly deteriorated and was transferred to the intensive care unit while awaiting the biopsy results. The biopsies showed very distinctive features compatible with HSV infection. The HSV IgG assay before liver transplantation was positive. Although we administered high-dose intravenous acyclovir immediately after the pathologic diagnosis, the patient died of severe septic shock on postoperative day 28. The possibility of HSV infection should be considered when atypical skin lesions occurring early after liver transplantation do not respond to antihistamines and steroids. An early diagnosis and the prompt administration of antiviral agents could prevent the fatal dissemination of an HSV infection in liver transplantation recipients.

Keywords: Herpes simplex virus; Viral infection; Liver transplantation; Immunosuppression; Opportunistic infections

INTRODUCTION

Liver transplantation has become the gold standard for the treatment of end-stage liver disease [1]. Although immunosuppressive agents after liver transplantation are essential for maintaining graft function, they also increase the incidence of various opportunistic infections [2]. Strenuous efforts have been made to detect opportunistic infections earlier and optimize immunosuppressant usage to counterbalance acute rejection and infectious complications [3]. However, infectious complications remain one of the leading causes of mortality after liver transplantation [4].

Herpes simplex virus (HSV) infection, categorized into HSV types 1 and 2, is ubiquitous and contagious in adults [5]. The clinical manifestations of HSV infection primarily present as orofacial, genital, or anal disease and are confined to a cutaneous lesion. However, it can occur in various tissues of the body [6]. HSV-induced hepatitis is a rare complication of HSV infection, often leading to severe liver failure [7]. While HSV infection is lifelong and can recur in immunocompetent patients, it is usually not fatal and is treatable with antiviral agents [8]. We report a case of rare but fatal systemic HSV infection with atypical clinical manifestations early after living donor liver transplantation.

CASE PRESENTATION

A 45-year-old female patient who suffered repeated large-volume paracentesis and recurrent esophageal variceal bleeding due to alcoholic liver cirrhosis with uncontrolled portal hypertension, underwent living donor liver transplantation using a left liver graft from an ex-spouse. The model for end-stage liver disease score prior to transplantation was 7, and the Child-Pugh grade was B at the time of transplantation. For immunosuppression, 20 mg of basiliximab and 500 mg of methylprednisolone were

administered during the operation. After surgery, the total bilirubin level and prothrombin time normalized rapidly, and the patient was transferred to the general ward on postoperative day (POD) 5. Triple regimen immunosuppressive agents consisting of tacrolimus, mycophenolate mofetil, and a steroid were administered. The trough tacrolimus level was maintained between 6–8 ng/mL during the postoperative period.

Mild erythematous erosive patches developed on both palms and soles on POD 12. The lesions were suspected to be hand-foot eczema or a skin reaction. Thus, topical desonide was applied based on the dermatologist's opinion. However, the extent and severity of skin lesions gradually worsened. Consequently, erythematous vesicles and papules with severe itching were increasingly scattered on the neck, arms, and trunk. The lesion did not respond to various topical steroids and antihistamines, so we decided to perform a skin biopsy. At the same time, aspartate aminotransferase, alanine aminotransferase, and total bilirubin levels, which had normalized, increased rapidly. Since the CT scan could not reveal the specific cause of liver dysfunction, such as hemodynamic abnormalities in the allograft and bile duct dilatation, we also performed a sonography-guided liver biopsy.

Despite intensive empirical antibiotic treatment while awaiting the biopsy results, the patient rapidly deteriorated and was transferred to the intensive care unit. A skin biopsy showed very distinctive features compatible with HSV infection (Fig. 1A). The liver biopsy also showed extensive confluent coagulative necrosis and viral cytopathic effects in the bile duct with positive immunohistochemical staining for HSV (Fig. 1B). The patient's HSV IgG assay was positive before liver transplantation. Although high-dose intravenous acyclovir (10 mg/kg daily during continuous renal replacement therapy) was administered immediately after the diagnosis, serious erosion and rash accompanied by

Fig. 1. (A) A skin biopsy showed acantholysis and multinucleated giant cells with ground-glass intranuclear viral inclusions and chromatin margination (x400, hematoxylin-eosin stain). (B) A liver biopsy demonstrated necrotic hepatocytes with viral cytopathic changes (x400, hematoxylin-eosin stain). The yellow arrow indicates multinucleated giant cells with ground-glass intranuclear viral inclusions and chromatin margination.

Fig. 2. Severe erosion and rash covered all body skin on postoperative day 28.

severe pain covered the skin of the entire body (Fig. 2). Finally, the patient died due to multiorgan failure on POD 28.

DISCUSSION

HSV infection is widespread worldwide. Although there are some regional differences, the prevalence of HSV-1 and HSV-2 was reported to be 66% and 12%, respectively, of the total population [9]. It primarily affects the skin and mucus membranes, irrespective of the type. For most immunocompetent hosts, an HSV infection is temporary and resolves without detrimental sequelae [8]. However, there have been several reports on visceral involvement in HSV infections [10,11]. In particular, HSV hepatitis can cause fatal acute liver failure even in immunocompetent hosts if it is not diagnosed in time [7]. Compromised cellular immunity after transplantation is a major risk factor for reinfection with and the recurrence of HSV [12]. One study reported that 42% of patients with positive HSV IgG before transplantation experienced changes of HSV polymerase chain reaction from negative to positive early after liver transplantation [13]. However, clinical manifestations of them were confined to oral mucosa and treated easily. In this case report, HSV infection might have resulted from the reactivation of a previous virus infection, considering that her HSV IgG assay was positive. It is unclear whether the origin site of the disseminated HSV infection was the skin or liver. However, considering the clinical course, in which liver failure occurred several days after the aggravation of skin lesions, HSV hepatitis was thought to be secondary vis-

ceral dissemination. Further, the HSV infection in our case report was likely to involve other organs as well as the skin and liver because the typical clinical presentations of HSV hepatitis are anicteric hepatitis without skin lesions [12].

There have been few reports on lethal HSV hepatitis in immunosuppressed hosts early after solid organ transplantation [10,14]. They have been reported the mortality rate of HSV hepatitis to 50% or more even with antiviral treatment. Most importantly, only the early detection and diagnosis of HSV infection can improve its prognosis. However, serologic analysis to detect antibodies has a limited role in diagnosing HSV infections because of its significant false-positive rate [15]. The most definite diagnostic modality is viral culture and pathologic diagnosis through biopsy. Histologic findings of HSV infection are very distinctive. It could be diagnosed when there are key features such as acanthosis with solitary keratinocytes and multinucleated giant cells with ground-glass intranuclear viral inclusions, suggesting viral cytopathic effects, even without immunohistochemistry [16]. In our case, we did not readily consider an HSV infection because the skin lesions initially appeared on the extremities, not on the orolabial, genital, or perianal area, where it typically begins. Patients with atypical skin lesions early after liver transplantation need to consult a dermatologist to discern suspected herpetic skin infection because atypical skin lesions are more frequent in immunosuppressed patients [17]. Furthermore, we should keep in mind the possibility of HSV infection when atypical skin lesions occurring in the early posttransplant period do not respond to topical steroids and antihistamines. In addition, if progressive aminotransferase elevations with coagulopathy occur in the early postoperative period without other problems, HSV hepatitis should be included in the differential diagnosis.

Transplant recipients have been reported to have severe clinical manifestations with visceral involvement and a slower response to antiviral treatment [18]. The urgent administration of high-dose acyclovir can avoid life-threatening outcomes. The empirical administration of acyclovir has to be considered for patients with symptoms suspicious of an HSV infection even before a definite diagnosis. In terms of prevention, many centers have implemented cytomegalovirus prevention protocols for high-risk patients using ganciclovir, acyclovir, valacyclovir, and valganciclovir [19]. These antiviral agents also have prophylactic effects against HSV replication. A previous study reported that severe HSV hepatitis disappeared after using prophylactic acyclovir [7]. According to the American Society of trans-

plantation infectious disease community of practice guidelines, HSV-specific antiviral prophylaxis should be administered for HSV-seropositive transplant recipients who are not receiving cytomegalovirus prophylaxis [18]. Further, it also could be considered when HSV-seronegative patients undergo liver transplantation with grafts from seropositive donors. Acyclovir at a dose of 200 mg three or four times a day is effective in HSV prophylaxis.

In conclusion, our case report presents a fatal and atypical HSV infection with systemic involvement early after living donor liver transplantation. We should consider HSV as a source of severe opportunistic infections and make efforts for prevention and an early diagnosis.

FUNDING

There was no funding related to this study.

CONFLICT OF INTEREST

All authors have no conflicts of interest to declare.

ORCID

Hye-Sung Jo	https://orcid.org/0000-0002-9253-8662
Pyoung-Jae Park	https://orcid.org/0000-0001-6624-7522
Wan-Joon Kim	https://orcid.org/0000-0002-4800-7573
Hyung Joon Han	https://orcid.org/0000-0002-7830-5352
Young-Dong Yu	https://orcid.org/0000-0003-3452-338X
Dong-Sik Kim	https://orcid.org/0000-0002-0608-1580

AUTHORS' CONTRIBUTIONS

Conceptualization: HSJ, PJP, DSK. Data curation: HSJ, PJP, WJK. Formal analysis: HSJ, PJP, YDY, DSK. Investigation: HSJ, PJP, WJK, HJH, YDY. Methodology: HJH, YDY. Project administration: DSK. Resources: PJP, WJK. Supervision: DSK. Writing - original draft: HSJ, PJP, WJK, HJH, YDY. Writing - review & editing: All.

REFERENCES

1. Sundaram V, Mahmud N, Perricone G, Katarey D, Wong RJ, Karvellas CJ, et al.; Multi-Organ Dysfunction, Evaluation for Liver Transplantation (MODEL) Consortium. Longterm outcomes of patients undergoing liver transplantation for acute-on-chronic liver failure. *Liver Transpl* 2020;26:1594-1602.
2. Garrido RS, Aguado JM, Díaz-Pedroche C, Len O, Montejo M,

- Moreno A, et al. A review of critical periods for opportunistic infection in the new transplantation era. *Transplantation* 2006;82:1457-1462.
3. Shaked A, DesMarais MR, Kopetskie H, Feng S, Punch JD, Levitsky J, et al. Outcomes of immunosuppression minimization and withdrawal early after liver transplantation. *Am J Transplant* 2019;19:1397-1409.
4. Laici C, Gamberini L, Bardi T, Siniscalchi A, Reggiani MLB, Faenza S. Early infections in the intensive care unit after liver transplantation-etiology and risk factors: a single-center experience. *Transpl Infect Dis* 2018;20:e12834.
5. Fatahzadeh M, Schwartz RA. Human herpes simplex virus infections: epidemiology, pathogenesis, symptomatology, diagnosis, and management. *J Am Acad Dermatol* 2007;57:737-763; quiz 764-766.
6. Staikov IN, Neykov NV, Kazandjieva JS, Tsankov NK. Is herpes simplex a systemic disease? *Clin Dermatol* 2015;33:551-555.
7. Kusne S, Schwartz M, Breinig MK, Dummer JS, Lee RE, Selby R, et al. Herpes simplex virus hepatitis after solid organ transplantation in adults. *J Infect Dis* 1991;163:1001-1007.
8. Brady RC, Bernstein DI. Treatment of herpes simplex virus infections. *Antiviral Res* 2004;61:73-81.
9. Looker KJ, Magaret AS, May MT, Turner KM, Vickerman P, Gottlieb SL, et al. Global and regional estimates of prevalent and incident herpes simplex virus type 1 infections in 2012. *PLoS One* 2015;10:e0140765.
10. Norvell JP, Blei AT, Jovanovic BD, Levitsky J. Herpes simplex virus hepatitis: an analysis of the published literature and institutional cases. *Liver Transpl* 2007;13:1428-1434.
11. Ishihara T, Yanagi H, Ozawa H, Takagi A. Severe herpes simplex virus pneumonia in an elderly, immunocompetent patient. *BMJ Case Rep* 2018;2018:bcr2017224022.
12. Riediger C, Sauer P, Matevossian E, Müller MW, Büchler P, Friess H. Herpes simplex virus sepsis and acute liver failure. *Clin Transplant* 2009;23 Suppl 21:37-41.
13. Griffiths WJ, Wreghitt TG, Alexander GJ. Reactivation of herpes simplex virus after liver transplantation. *Transplantation* 2005;80:1353-1354.
14. Côté-Daigneault J, Carrier FM, Toledano K, Wartelle-Bladu C, Willems B. Herpes simplex hepatitis after liver transplantation: case report and literature review. *Transpl Infect Dis* 2014;16:130-134.
15. Singh A, Preiksaitis J, Ferenczy A, Romanowski B. The laboratory diagnosis of herpes simplex virus infections. *Can J Infect Dis Med Microbiol* 2005;16:92-98.
16. Yamamoto T, Aoyama Y. Detection of multinucleated giant cells in differentiated keratinocytes with herpes simplex virus and varicella zoster virus infections by modified Tzanck

- smear method. *J Dermatol* 2021;48:21-27.
17. Fernandez-Nieto D, Jimenez-Cauhe J, Ortega-Quijano D, Burgos-Blasco P, Pindado-Ortega C, Bea-Ardebol S. A case of atypical disseminated herpes simplex virus 1 with hepatitis in a liver transplant recipient: the need for dermatologic evaluation. *Dermatol Online J* 2020;26:13030/qt3k90n5s9.
 18. Lee DH, Zuckerman RA; AST Infectious Diseases Community of Practice. Herpes simplex virus infections in solid organ transplantation: guidelines from the American Society of Transplantation Infectious Diseases Community of practice. *Clin Transplant* 2019;33:e13526.
 19. Preiksaitis JK, Brennan DC, Fishman J, Allen U. Canadian Society of Transplantation consensus workshop on cytomegalovirus management in solid organ transplantation final report. *Am J Transplant* 2005;5:218-227.