A case of atypical disseminated herpes simplex virus 1 with hepatitis in a liver transplant recipient: the need for dermatologic evaluation
Case Presentation

A case of atypical disseminated herpes simplex virus 1 with hepatitis in a liver transplant recipient: the need for dermatologic evaluation

D Fernandez-Nieto MD, J Jimenez-Cauhe MD, D Ortega-Quijano MD, Patricia Burgos-Blasco MD, Cristina Pindado-Ortega MD, S Bea-Ardebol MD PhD

Affiliations: Department of Dermatology, Hospital Universitario Ramón y Cajal, Madrid, Spain

Corresponding Author: Diego Fernandez-Nieto MD, Department of Dermatology, Hospital Universitario Ramón y Cajal, Madrid, Spain, University of Alcalá de Henares, Madrid, Spain, Tel: 34-699375743, FAX: 34-913368582, Email: fnietodiego@gmail.com

Abstract

Disseminated herpes simplex virus (HSV) is mainly seen in immunocompromised individuals. Atypical lesions can be present in both primary infection and reactivation disease. Compared with the general population, immunocompromised hosts are at greater risk of increased persistency and severity of clinical manifestations, including severe systemic involvement such as esophagitis, meningitis, and hepatitis. Herein, we report the case of a liver transplant recipient with atypical disseminated herpes simplex virus-1 complicated by HSV-related hepatitis. Dermatological consultation and histological assessment were crucial for a correct diagnosis and treatment.

Keywords: herpes simplex, viral disease, hepatitis, immunosuppression, organ donor recipient

Introduction

Herpes simplex virus (HSV) hepatitis is usually characterized by a non-specific presentation, making timely diagnosis difficult. Less than 50% of individuals present with typical skin or mucosal findings [1]. Herein, we report a patient with atypical disseminated HSV-1 with hepatic involvement in which dermatological evaluation was key to ensure accurate diagnosis and appropriate treatment.

Case Synopsis

A 53-year-old man was admitted to our hospital with a 3-week-history of continuous fever of up to 38.2°C, with no symptoms other than mild fatigue. His past medical history included a liver transplant 15 years prior owing to viral hepatitis-related cirrhosis, portal vein thrombosis, stage-3 chronic kidney disease, and bilateral avascular hip necrosis. His medication included tacrolimus 1mg/day, mycophenolate mofetil 500mg BID, prednisone 2.5mg every other day, and acenocoumarol 1mg/day. The patient was prescribed full-spectrum antibiotic coverage with meropenem and vancomycin without improvement. Scarce asymptomatic skin lesions of the left malar region appeared 7 days after the onset of the fever and these were initially assumed to relate to unrecognized minor trauma. On the 14\textsuperscript{th} day, isolated vesicles and blisters appeared on fingers and some days later on the right foot. Physical examination revealed a crusted hemorrhagic erosion on the left malar region (Figure 1A), scarce hemorrhagic crusts on the dorsal aspects of the fingers (Figure 1B), a hemorrhagic blister on the 5\textsuperscript{th} left finger (Figure 1C), and a vesicle with clear fluid contents on the medial aspect of the right foot (Figure 1D). No other skin or mucosal lesions were noted. The patient denied previous history of HSV or aphthous ulcers.

Laboratory tests revealed a hepatic disfunction (AST 425U/L, ALT 202U/L, GGT 1053U/L, total bilirubin 1.5mg/dL), metabolic acidosis (pH 7.26), and moderate leukopenia (3100×10\textsuperscript{3/μL}) with lymphopenia (350×10\textsuperscript{3/μL}). Blood cultures were consistently negative. Ultrasonography revealed several punctiform hepatic lesions, which were hypermetabolic on the subsequent positron
emission tomography-computed tomography (PET-CT) images. There were no other remarkable findings. Skin 4mm punch biopsies were performed from the malar and the foot lesions (Figure 2), revealing spongiosis with ballooning degeneration of keratinocytes and multinucleated giant cells. Multiplex PCR assay for detecting herpesvirus DNA was obtained from skin lesions and blood samples; both showed positivity for herpes simplex virus 1 (HSV-1). Intravenous acyclovir adjusted to renal function was started. After 14 days of treatment we observed an excellent response, with a return to normal laboratory and image tests, remission of fever, and complete resolution of skin lesions.

**Case Discussion**
Herpes simplex virus-1 or HSV-2 hepatitis is mainly seen in immunocompromised individuals. The most common patients are recipients of organ
transplantation, which represent around 30% of those affected. This is a particular risk after transplantation. In addition to transplantation patients, 23% of HSV hepatitis occurs in immunosuppressed patients by other causes and another 23% in pregnant women, whereas only 24% of HSV hepatitis cases occur in immunocompetent individuals [2]. Moreover, within liver transplantation recipients, mycophenolate mofetil has been associated with a particularly increased risk of HSV reactivation over other immunosuppressive drugs [3].

Around 74% of HSV hepatitis cases result in acute liver failure. This can result in emergent need for liver transplantation with high mortality rates of >80% in untreated patients and >50% in those treated with acyclovir, making timely diagnosis essential [4]. In patients receiving liver transplantation, HSV reactivation occurs more commonly during the first month after transplantation, making a diagnosis of HSV difficult owing to overlapping features of acute organ rejection during this time period [5].

Severe forms of disseminated HSV disease include mucocutaneous or visceral manifestations, such as esophagitis, hepatitis, and pneumonitis. Fever, leukopenia, hepatitis, and encephalitis are all common presenting signs of disseminated disease. In HSV-related hepatitis, blood tests show elevated transaminase levels in 70% of cases, reaching levels of 1000-fold over the upper normal limit in fulminant hepatitis. Patients are usually anicteric with low-to-normal bilirubin levels [6]. Both the risk of severe HSV infection and HSV disease recurrence rate correlate with defects of T cell immunity competence. Patients with mild decreases in cellular immunity may experience only an increased number of recurrences and a longer duration of lesions, whereas severely compromised patients are more likely to develop disseminated, chronic, or drug-resistant infections [7].

The utility of serology including IgM and IgG antibodies for HSV is limited owing to false positive and false negative results. However, HSV DNA PCR performed on blood samples is a rapid test with a greater sensitivity and specificity than HSV antibodies [1]. To confirm the diagnosis of HSV hepatitis, liver biopsy can be considered. However, there is an increased risk of bleeding associated with liver biopsy in patients with acute liver failure. Therefore, it is important to weigh risks against benefits [8]. Few case reports mention the role of computed tomography (CT) in diagnosing HSV hepatitis. The presence of diffuse multiple hypodense lesions of 1–3mm along with hepatomegaly can be seen in HSV-related hepatitis. These lesions represent focal areas of necrosis.

*Figure 2. Histopathology from the vesicle on the right foot. Spongiotic vesicle with ballooning degeneration of keratinocytes, steel-grey nuclei, and multinucleated giant cells. A mild neutrophilic infiltrate is present. (H&E, 40×).*
related to viral infection. However, these features are not specific for HSV hepatitis [9].

Dermatological examination is essential to discern any suspected herpetic lesions. Atypical unrecognized presentation forms are more frequent in immunosuppressed patients who are also at greater risk of disseminated disease and a fulminant course. Moreover, the differential diagnosis of skin lesions in an immunocompromised patient with fever includes other life-threatening infections and noninfectious diseases such as septic emboli, angioinvasive fungal infections, vasculitis, or vasculopathic processes such as disseminated intravascular coagulopathy.

In the present case, skin lesions were noted two weeks after the onset of symptoms and not before, which is uncommon. It is possible that the few asymptomatic lesions were not recognized at first. In addition, the overall picture was less severe and more persistent than what is usually seen in HSV-related hepatitis, which is mild hepatic involvement and rapid full recovery.

**Conclusion**

Disseminated HSV infection is more common in immunosuppressed hosts, who have a greater risk of complications and morbidity and mortality. Atypical presentations are not uncommon and can delay diagnosis. We present a patient with atypical disseminated HSV with hepatitis in which dermatologic assessment was crucial to reach prompt diagnosis and adequate treatment. HSV should be considered in the differential diagnosis of immunocompromised patients with fever and skin lesions.

**Potential conflicts of interest**

The authors declare no conflicts of interest.

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**References**