Acute Liver Failure from Herpes Simplex Virus in an Immunocompetent Patient Due to Direct Inoculation of the Peritoneum

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ABSTRACT
Herpes simplex virus (HSV) hepatitis is a rare cause of acute liver failure (ALF). It carries a mortality rate of 80% if untreated, thus early identification and treatment are critical. Without high clinical suspicion, HSV hepatitis is difficult to diagnose. A 48-year-old Hispanic female presented with a 4-day history of abdominal pain and a vaginal cuff tear requiring laparoscopic repair. She subsequently developed postsurgical disseminated HSV, resulting in ALF. Acyclovir was initiated, but she was resistant to treatment. She was given additional foscarnet and responded without requiring a liver transplant.

INTRODUCTION
Acute liver failure (ALF) is an uncommon outcome of herpes simplex virus (HSV) infection, which was first described in adults in 1969. Immunocompromised and pregnant women are most commonly affected, but immunocompetent patients can rarely present with HSV hepatitis. The lack of mucocutaneous lesions in some patients often makes this diagnosis difficult. It can result in emergent need for liver transplant and high mortality rates of >80% in untreated patients and >50% in those treated with acyclovir (ACV). Early treatment with intravenous (IV) ACV is critical. Approximately 0.27% of immunocompetent patients are ACV-resistant versus 7% of their immunocompromised counterparts, who may require treatment with foscarnet. Encephalopathy due to ALF is often difficult to differentiate from an infectious intracranial etiology, hence a diagnostic lumbar puncture should be considered in patients who do not respond to conventional therapy.

CASE REPORT
A 48-year-old immunocompetent Hispanic female, with a history of total laparoscopic hysterectomy and uterosacral suspension 5 months prior to presentation, presented with a 4-day history of worsening hypogastric abdominal pain. She reported coitus with her partner prior to the onset of symptoms and denied barrier protection. On exam, temperature 98.2°F, heart rate 128 beats/minute, respiratory rate 16 breaths/minute, and blood pressure 111/76 mmHg. She had asterixis, vaginal cuff dehiscence, and multiple tender vaginal ulcers with clean bases, concerning for herpes infection. During laproscopic repair of the vaginal cuff, surgeons noted lesions that appeared to be herpetic on the bowel, semi-adherent to vaginal cuff. On post-operative day 1 (POD1), she developed elevated liver enzymes, consistent with hepatocellular insult, which continued to worsen. On POD4 she went into fulminant hepatic failure with hepatic encephalopathy and was transferred to our institution for liver transplant evaluation.

On admission, the patient had aspartate aminotransferase and alanine aminotransferase of 192 and 137 mg/dL, respectively, which subsequently peaked at 20,692 and 6,398 mg/dL on POD4. On admission, her international
normalized ratio was 1.0 and peaked at 2.9 on POD5. Her total bilirubin was 0.2 initially and peaked at 8.5 mg/dL on POD8. The acute viral serologies for hepatitis A, B, and C were negative, but serum HSV workup showed positivity for immunoglobulin M (IgM) and polymerase chain reaction (PCR). Abdominal ultrasound and computed tomography (CT) showed an enlarged liver (18 cm) with heterogeneous attenuation and a thickened peritoneum with large deposits along the pelvic wall, consistent with peritonitis. Her initial model-end stage liver disease score was 17, which subsequently peaked at 23 on POD5. On POD8, her aspartate aminotransferase and alanine aminotransferase trended down to 223 and 233 mg/dL, respectively.

Her initial complete blood count showed a white blood cell count of $3.65 \times 10^3$ cells/µL, hemoglobin 11.2 g/dL, and platelet count 146,000/µL. After 10 days of IV ACV therapy, her liver function tests dramatically improved, but her encephalopathy persisted, mandating further workup. Head CT showed subcortical focal hypodensities in the left frontal and parietal region, which was concerning for infarcts. Subsequent magnetic resonance imaging did not show any findings consistent with infarcts, but it did show juxtacortical and periventricular white matter signal abnormality in the parietal lobes, which were of nonspecific etiology. Lumbar puncture with cerebrospinal fluid analysis was significant for HSV and was PCR-positive with lactate dehydrogenase 1,593 U/L, glucose 73 mg/dL, total protein 66 mg/dL, red blood cell count of 1,035 cells/mm³, and total white blood cell count of 0 cells/mm³. Initial dosing of ACV was adequate for the treatment of encephalitis as well, so we considered this to be ACV-resistant HSV and added IV foscarnet (60 mg/kg every 12 hours for 14 days). Her mental status improved markedly within 24 hours of starting foscarnet. The added treatment improved her mental status, and she did not require a liver transplant. After a prolonged hospital course of 2 months, she was discharged to subacute rehab and then home.

**DISCUSSION**

HSV hepatitis is rare in immunocompetent adults, with few reported cases. Due to its rarity, there are no societal guidelines for the diagnosis of HSV hepatitis, making patient history, physical examination, and strong clinical suspicion crucial. HSV hepatitis is usually characterized by signs of ALF, with serum transaminase levels 100–1,000-fold above normal. A wide variety of lab tests are available to aid in diagnosing HSV hepatitis, including liver biopsy, antigen detection test, viral culture, and nucleic acid detection with PCR. Despite the availability of multiple laboratory tests, their utility is low in guiding early empiric therapy. A review found that more than 50% of the cases were diagnosed using autopsy, while only 8% cases had serological confirmation. Our patient had active lesions on her vulva and had a positive HSV-2 IgM serology with negative HSV-2 IgG at the time of presentation. She subsequently had seroconversion of antibody status, consistent with primary infection. Other etiologies of fulminant liver failure, such as ischemic hepatopathy secondary to HSV encephalitis, were considered, but this differential was low given that the patient had no hemodynamic instability and had marked improvement in liver function with ACV therapy. Due to the rapid improvement with ACV treatment and the high risk of a liver biopsy due to substantial coagulopathy, a liver biopsy was not performed.

Mortality and hospital stay decreases with early treatment with ACV. In addition, early ACV treatment resulted in fewer cases of ALF requiring transplantation (51% vs. 88.1%). Our patient’s ALF improved with ACV, but her encephalopathy persisted. We suspected ACV resistance after 10 days of treatment without improvement of mentation. This case emphasizes the importance of considering additional treatments for HSV encephalopathy in patients who fail to respond to initial therapy.

ACV is classified as a category B drug in pregnancy with no difference in birth defects when compared to the general population. Given the high mortality of patients with HSV ALF, we believe that those who are pregnant or immunocompromised should be considered for empiric therapy. HSV infections with resistance to ACV are mainly reported in immunocompromised patients, with the prevalence varying from 3.5 to 10%. ACV resistance (even up to >25%) has been reported in bone marrow or allogeneic hematopoietic stem cell transplant recipients. Although some of these viral isolates were susceptible to ACV, some patients required foscarnet to resolve their mucocutaneous lesions. Currently, ACV resistance can only be tested using MRC-5 cell
mediums, and an expedient method is yet to be developed. In conclusion, our case illustrates an unusual presentation of HSV hepatitis. Diagnosis requires a high index of clinical suspicion. Early initiation of ACV is crucial for treatment. Duration of anti-viral treatment remains unclear, but continuation of therapy until resolution of symptoms, improvement in liver function tests, and negative serum PCR is advisable. Our report demonstrates the need to add a second antiviral, in this case foscarnet, in an immunocompetent patient with a resistant infection.

DISCLOSURES
Author contributions: All authors wrote and edited the manuscript. D. Chaudhary is the article guarantor.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received July 19, 2016; Accepted November 28, 2016

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