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Disseminated Herpes Simplex Virus-2 (HSV-2) as a Cause of Viral Hepatitis in an Immunocompetent Host

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 57-year-old
Final Diagnosis: Hepatitis • herpes
Symptoms: Fever
Medication: —
Clinical Procedure: —
Specialty: General and Internal Medicine

Objective: Challenging differential diagnosis

Background: Herpes simplex virus-2 (HSV-2) affects nearly 1 in 5 adults in the United States. Complications such as viral hepatitis and dissemination are rare in immunocompetent hosts. In this report, we describe a case of viral hepatitis secondary to disseminated HSV-2 in an immunocompetent patient with recurrent fevers and elevated aminotransferases.

Case Report: A 57-year-old man with a history of type 2 diabetes and hypertension was admitted with a right index finger lesion concerning for an abscess. He underwent successful incision and drainage and was started on ampicillin-sulbactam. On Day 2 of hospitalization, he developed recurrent fevers and elevated aminotransferases and inflammatory markers. An extensive infectious, rheumatologic, and malignancy workup were pursued without immediate findings. Imaging demonstrated cirrhotic morphology of the liver and splenomegaly, but lab markers were intact for liver synthetic function. On Day 7 of hospitalization, fever frequency decreased, and HSV-2 titers resulted, with positive IgM and negative IgG. He subsequently developed erythematous, raised lesions in multiple dermatomes. Nucleic acid amplification testing of biopsied lesions was positive for HSV-2, confirming viral hepatitis secondary to disseminated HSV-2. He was started on intravenous acyclovir and discharged on valacyclovir following improvement in symptoms.

Conclusions: We report a case of viral hepatitis secondary to disseminated HSV-2 in an immunocompetent host. Up to 25% of cases occur in immunocompetent hosts and many patients do not develop characteristic skin lesions. Early diagnosis and treatment of viral hepatitis secondary to disseminated HSV remains vital to minimize morbidity and mortality.

Keywords: Hepatitis • Herpes Simplex • Leukopenia

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/932474

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Background

Herpes simplex virus-2 (HSV-2) is a common sexually transmitted disease known to cause genital lesions. It is estimated that nearly 1 in 5 adults in the United States has HSV-2, with an annual incidence of one million cases per year [1,2]. Seroprevalence rates are estimated near 16% in those aged 14-49 [3]. Despite the prevalence of HSV-2, complications such as viral hepatitis and dissemination remain rare in immunocompetent hosts. In this report, we describe a rare case of viral hepatitis secondary to disseminated HSV-2 in an immunocompetent patient with recurrent fevers and elevated aminotransferases. Disseminated HSV-2 was diagnosed following positive IgM serologies and interval development of vesicular lesions.

Case Report

A 57-year-old man with past medical history of hypertension and diabetes mellitus type 2 presented to the emergency room (ER) with right index finger pain. Three days prior to admission, the patient cut his right index finger while sorting ballots. In the following days, he noted worsening swelling and pain in the finger causing him to present to the ER. At the time of presentation, he was afebrile, with a heart rate of 87 beats per minute, respiratory rate of 16 breaths per minute, blood pressure of 143/82 mmHg, and oxygen saturation of 97% on room air. The physical exam was notable for a 1-cm raised lesion over the dorsal aspect of the distal interphalangeal joint on the index finger (**Figure 1**). Complete blood cell count demonstrated a platelet count of 91×10^3 cells/μL and the basic metabolic panel was unremarkable. The patient was evaluated by the orthopedics team, who performed a bedside incision and drainage. Purulent drainage was expressed and sent for culture. The patient was started on ampicillin-sulbactam and admitted to the orthopedic service for further care.

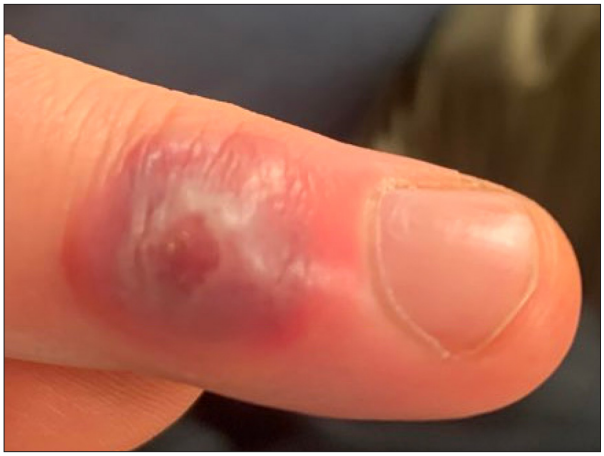

Figure 1. Right erythematous papule on initial presentation was thought to be an abscess.

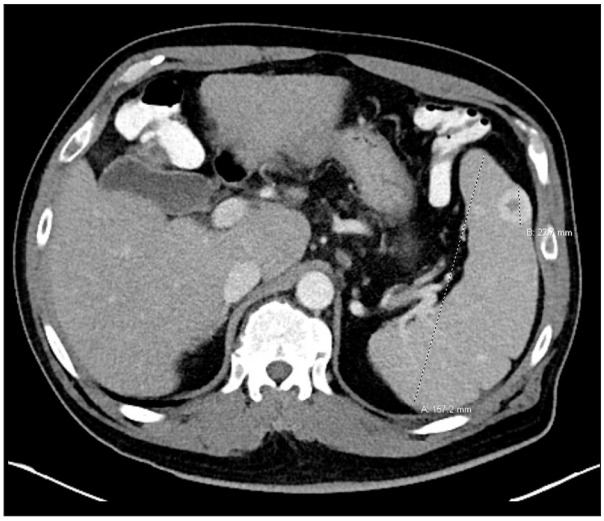

Figure 2. CT Abdomen and pelvis demonstrating cirrhotic morphology of the liver, splenomegaly, and splenic lesions.

On Day 2 of hospitalization, he developed multiple fevers daily, up to 39.5°C, despite continuation of ampicillin-sulbactam. White blood cell count and platelet count were reduced to 3.4×10^3 cells/μL and 80×10^3 platelets/μL, respectively, while the aminotransferases aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were markedly elevated (AST: 270 U/L, ALT: 332 U/L). The inflammatory markers C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and ferritin were also elevated to 108.3 mg/L, 83 mm/h, and 517 ng/mL, respectively. Given elevated inflammatory markers and multiple fevers daily, our infectious diseases (ID) team was consulted, and the patient was transferred to our hospitalist service for further workup. Upon further questioning, the patient noted he had experienced intermittent night sweats 2 days prior to admission. He denied any known sick contacts, recent cough, shortness of breath, abdominal pain, diarrhea, dysuria, joint pain, lymphadenopathy, known sick contacts, or other rashes/lesions. The patient had no history of recurrent infections, immunodeficiency, known allergies to medication, or previous steroid use. He worked in local government and had no recent travel history. The patient consumed alcohol 3 to 5 times per week, 3 drinks at a time, and was sexually active with 2 female partners, intermittently using barrier protection. Family history was significant for inflammatory bowel disease and multiple sclerosis in his 2 sisters, but no history of malignancy was noted.

At the time of transfer to the hospitalist service, the patient's ampicillin-sulbactam had been discontinued. He was subsequently transitioned to doxycycline empirically to cover potential atypical infections, including tick-borne illnesses. Viral and further infectious workup was thus far negative,

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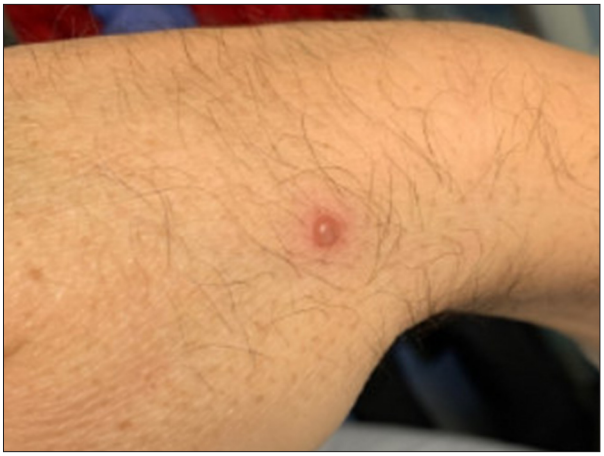

Figure 3. 4 mm clear vesicle with erythematous base on right ulnar dorsal hand.

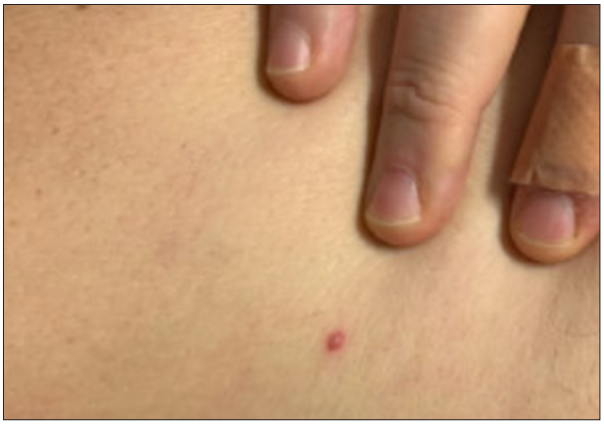

Figure 4. 3 mm vesicle with erythematous base on right medial thigh.

including SARS-CoV-2 PCR, *Borrelia* IgG/IgM, *Anaplasma* IgG, *Babesia* IgG, *Ehrlichia* IgG, West Nile Virus IgM, *Rickettsia* IgG, HIV, Procalcitonin, Hepatitis A IgM, Hepatitis B surface antigen, Hepatitis C antibody, QuantiFERON-Plus for tuberculosis, urine *Streptococcus pneumoniae* and *Legionella* antigen, wound cultures, and blood cultures. Due to inconclusive diagnostic tests and lack of clinical improvement, doxycycline was discontinued. A computed tomography (CT) scan of the chest, abdomen, and pelvis was obtained to assess for malignancy or localized infectious etiology. Findings were notable for cirrhotic morphology of the liver, an enlarged spleen concerning for portal hypertension, and splenic lesions, of which the largest was 22.7 mm (**Figure 2**). Multiple indeterminant enhancing splenic lesions were also noted that were read as possible hemangiomas or hematomas. Inflammatory markers and aminotransferases continued to rise with CRP, ferritin, AST, and ALT peaking at 131.9 mg/L, 4391 ng/mL, 377 U/L, and 515 U/L, respectively.

Given the complexity of the case, a multi-disciplinary approach was taken, with the involvement of the

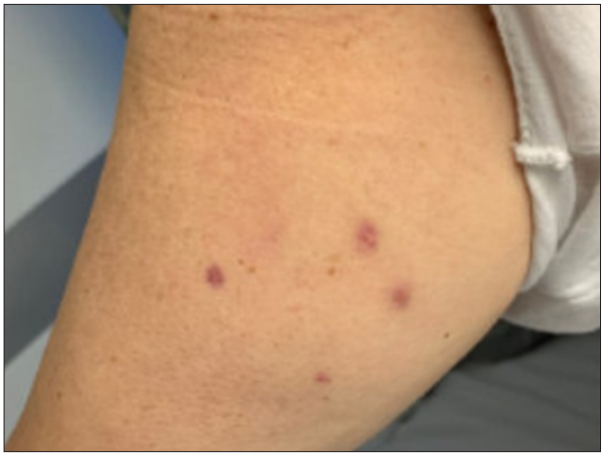

Figure 5. 4-7 mm multiple erythematous macules on left tricep.

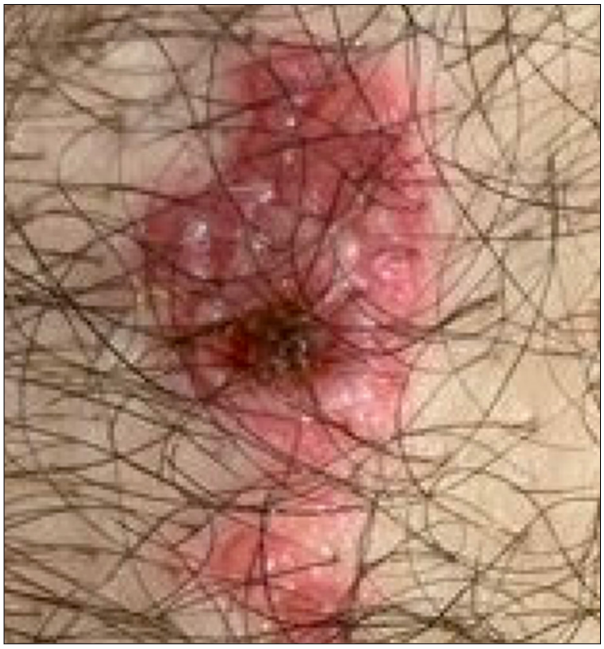

Figure 6. Multiple tiny vesicles with crusting overlaying suprapubic region.

hospitalist, ID, hepatology, rheumatology, and hematology teams. Hemophagocytic lymphohistiocytosis (HLH) was considered, given the constellation of his symptoms; however, he only met 3 of the necessary 5 criteria needed for diagnosis (fever, splenomegaly, and elevated ferritin). Rheumatologic workup was also negative, including antinuclear antibody, complement factor 3, complement factor 4, myeloperoxidase, and proteinase 3. A broad workup for his transaminitis was pursued, including viral etiologies such as cytomegalovirus (CMV), Epstein-Barr virus, and HSV. Finally, a whole-body gallium scan was obtained to assess for any potential source of infection given findings of splenic lesions on CT. The abdomen gallium scan results demonstrated no areas of localized uptake.

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On Day 7 of hospitalization, the patient's frequency of fevers decreased to 1 to 2 times a day. He was also found to have new erythematous, raised lesions on his right wrist (**Figure 3**), right medial thigh (**Figure 4**), left triceps (**Figure 5**), suprapubic area (**Figure 6**), and right posterior auricular region. At this time, HSV-2 titers were detected, with positive IgM and negative IgG, consistent with acute primary infection. Nucleic acid amplification testing from biopsied skin lesions was positive for HSV-2. The patient was placed on contact precautions and started on intravenous acyclovir 400 mg every 8 h. Inflammatory markers, including ferritin, CRP, ESR, and liver enzymes continued to downtrend with subsequent improvement in his fever curve as well. He was discharged home on valacyclovir 1000 mg 3 times per day by mouth and instructed not to return to work or have close contact with other individuals for 5 to 7 days, given that the lesions had not scabbed over. He was seen in the ID outpatient clinic 1 week after hospital discharge and noted improvement in his symptoms. HSV-2-related lesions had scabbed over and valacyclovir was reduced to 1000 mg twice a day with planned completion of a total antiviral course of 14 days. Followup HSV-2 serum titers confirmed seroconversion with positive HSV-2 IgG titers and falling IgM titers, further validating a primary HSV-2 infection.

Discussion

Our case highlights the importance of considering disseminated HSV as a differential diagnosis for recurrent fevers and elevated aminotransferases, even in patients without classic skin findings. HSV-2 remains a common sexually transmitted disease in the United States, and most often presents with genital lesions. Primary infection occurs when an individual is exposed to another who is actively shedding the virus from their skin or secretions. Following initial exposure, the virus typically has a 4-7-day incubation period that may be accompanied by itching or burning at the exposure site prior to development of classic vesicular lesions [1,4]. It is important, however, to note that many patients may not develop characteristic lesions following primary infection. In a survey of New York City residents performed in 2004 to determine HSV-2 seroprevalence, Schillinger et al found that nearly 28% of surveyed individuals were infected with HSV-2, of which 88.4% had no prior knowledge of diagnosis [5]. Our patient presented with a lesion on the right index finger, which was initially thought to be an abscess based upon history and notable purulent drainage. In hindsight, the lesion was likely a herpetic whitlow and representative of an acute herpetic process. However, lack of assessment of this lesion by the primary team and the absence of other cutaneous signs of herpes infection delayed the consideration of disseminated HSV by more than 6 days.

Our case is of particular interest given the rarity of viral hepatitis secondary to disseminated HSV-2 in an immunocompetent host. Viral hepatitis accounts for only 1-2% of all viral causes of acute liver failure [6-10]. Risk factors for disseminated disease include immunodeficiency, immunocompromised state, post-transplantation, and pregnancy (primarily in the third trimester); however, up to 25% of cases occur in immunocompetent patients [8]. HSV hepatitis remains difficult to diagnose given the nonspecific nature of presenting signs and symptoms. Most commonly, patients present in an anicteric state with elevated aminotransferases, low bilirubin, leukopenia, and thrombocytopenia with concurrent fever or abdominal pain [9-14]. Although peak aminotransferases are often greater than 1000, values less than 1000 can be seen [15]. The constellation of these signs and symptoms can also mimic other rare cytokine-induced states, such as HLH, and can lead to a broad workup as seen in our patient. Disseminated HSV-2 has been shown to cause HLH-like syndromes, and differentiating between them remains important, as empiric high-dose immunosuppression could worsen HSV-2 [16]. Our patient met 3 of the necessary 5 criteria for HLH, and steroids were not given. We also highlight that only 30-50% of patients present with, or develop, characteristic herpetic lesions, further emphasizing that clinicians should not rely on classic cutaneous findings in diagnosing disseminated HSV [9]. Early diagnosis and treatment with intravenous acyclovir remains essential as 74% of cases progress to acute liver failure, with mortality rates as high as 90% [7-10,12,13,17].

Cases of viral hepatitis secondary to disseminated HSV in immunocompetent patients have been described in the literature [18-29], many of which resulted in acute liver failure. The pathophysiology driving dissemination of HSV in immunocompetent hosts remains unclear. In their case report, Miyazaki et al proposed 4 possible mechanisms for dissemination in the immunocompetent host: 1) host immunological defenses overwhelmed by HSV viremia at initial infection, 2) occult defects in T cell and macrophage processing of HSV antigens, 3) reinfection by a second strain of HSV, and 4) heterogeneity in HSV strains [21].

Although no primary immunodeficiencies were noted in our patient, CT of the abdomen did demonstrate a cirrhotic morphology of the liver. This may suggest an acquired immunodeficient state, as cirrhosis can be associated with several abnormalities in both innate and adaptive immune response due to underlying changes in the liver architecture. This can impact the function of circulating immune cells, leading to decreases in naïve, memory T helper cells, and cytotoxic T cells even in the early stages of cirrhosis [30-33]. These findings, however, are much more heightened and prevalent in a decompensated state, which was not evident in our patient [31]. It remains unclear whether our patient had true cirrhosis versus late-stage fibrosis, given that markers of liver synthetic function were not deranged, aminotransferases continued to downtrend as he underwent followup as an outpatient, and acuity of the disseminated HSV-2 may have contributed to the

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cirrhotic morphologic appearance on imaging. Further workup, however, would be required to confirm cirrhosis diagnosis and substantiate if this may have played a role in developing the disseminated HSV-2 in our patient.

Conclusions

Early diagnosis and treatment of viral hepatitis secondary to disseminated HSV remains vital to minimize morbidity and mortality. Although signs and symptoms can be nonspecific, HSV hepatitis must be considered in those with recurrent fevers, elevated aminotransferases, leukopenia, and thrombocytopenia. The constellation of these findings was crucial for the diagnosis in our patient, and early treatment with acyclovir likely improved the outcome. It is also important to highlight the need for a high index of suspicion given that most patients develop characteristic mucocutaneous lesions late in their presentation. Many patients will not develop skin lesions at all, and up to 25% of cases occur in immunocompetent hosts. Similarly, in our patient, cutaneous lesions were a late finding in our patient's presentation, and the workup for primary immunodeficiency was negative. The incidental finding of cirrhosis may have represented an acquired immunodeficient state in our patient; however, further studies are needed to validate such correlations.

Conflict of Interest

None .

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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