

# Acquired Hemophagocytic Lymphohistiocytosis Associated With Disseminated Herpes Simplex Virus in Immunocompetent Host

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## ABSTRACT

We report the case of an immunocompetent young woman who developed multisystem organ failure following herpes simplex virus type 2 and hemophagocytic lymphohistiocytosis. Despite intravenous acyclovir and supportive measures, she rapidly progressed to acute liver failure and died before she could receive orthotopic liver transplant.

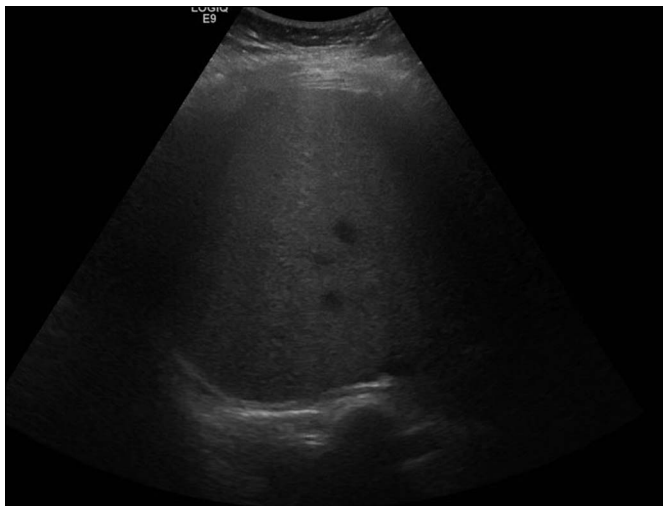
## INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare, but often life-threatening illness that typically affects children and young adults. HLH is a hyperinflammatory state that is characterized by excessive activation of lymphocytes and histiocytes, resulting in an overwhelming but ineffective immune response. The early symptoms of HLH are nonspecific, including fever, hepatosplenomegaly, rash, jaundice, lymphadenopathy, and various cytopenias.<sup>1</sup> Viral infections appear to be the most common trigger for secondary HLH and present a diagnostic challenge since the viral entity may mimic the early signs of HLH, without evolving into the disease itself.<sup>2,3</sup> Clinicians should be familiar with the distinct clinical and laboratory features of HLH.

## CASE REPORT

A 27-year-old Hispanic woman with a past medical history of obesity and newly onset diabetes mellitus type 2 presented to an outside facility with 3 days of fever, dysuria, and abdominal pain. She had been sexually active with a new partner for the past 4 months and admitted to not using barrier contraception. She received outpatient treatment for a urinary tract infection with sulfamethoxazole/trimethoprim but shortly returned to the emergency department due to flank pain and worsening symptoms. Laboratory test results at the outside hospital revealed rapidly rising transaminitis and pancytopenia. Abdominal ultrasound showed fatty liver changes and mild splenomegaly measuring up to 13 cm (Figure 1). The patient was subsequently transferred to our tertiary center for higher level of care and due to concern for progressive acute liver injury.

Upon arrival, the patient was nontoxic appearing and did not show evidence of hepatic encephalopathy. Biochemical parameters on admission were as follows: aspartate aminotransferase 6,062 U/L, alanine aminotransferase (ALT) 2,454 U/L, total bilirubin 3.5 mg/dL, and ammonia 203 µg/dL. Physical examination was significant for right upper quadrant tenderness and mucocutaneous rash. She had numerous shallow, ulcerative facial lesions with an area of crusting to the left lateral commissure of the lip (Figure 2). The tongue was covered by multiple plaque-like ulcerative lesions with central clearing. Intravenous acyclovir (10 mg/kg every 24 hours) was started empirically for suspected herpes simplex virus (HSV) hepatitis based on the classic morphology of cutaneous lesions. Over the course of 2 days, the patient's clinical status quickly deteriorated. She developed worsening confusion and asterixis, indicative of progression to acute liver failure (ALF). Ammonia levels reached a peak of 564 µg/dL and international normalized ratio was 3.02, while aspartate aminotransferase and ALT continued to increase to 12,280 and 3,502 U/L, respectively. The patient became hypotensive and encephalopathic, requiring intubation for airway protection and vasopressors to maintain perfusion. Unfortunately, the patient was deemed too unstable to undergo liver transplant. Rectal and throat swab of ulcerative lesions returned



**Figure 1.** Ultrasound image of the right upper quadrant showing fatty liver disease.

positive for HSV-2 by polymerase chain reaction. Serum HSV-2 IgG was also positive. It was suspected that initial dysuria on presentation was a consequence of genital lesions rather than a true urinary tract infection. Cytomegalovirus, Epstein–Barr virus, human immunodeficiency virus, hepatitis serologies, parvovirus B19, and varicella-zoster virus were all negative. Autoimmune workup was negative as well.

The patient's pancytopenia was originally thought to be a sequela of viral infection. Complete blood count showed a nadir of  $0.59 \times 10^3/\text{cm}^3$  white blood cells (absolute neutrophil count  $0.33 \times 10^3/\text{cm}^3$ ), platelets 17,000 per  $\mu\text{L}$ , and hemoglobin 6.9 g/dL. Upon further investigations, ferritin was greater than 40,000 ng/mL, fibrinogen was 99 mg/dL, lactate dehydrogenase was greater than 6,000 U/L, and serum triglycerides were 206 mg/dL. Although intravenous acyclovir improved her blood counts, the overwhelming inflammatory response secondary to suspected HLH and concomitant liver failure from herpes simplex virus resulted in multiorgan failure. The patient went into cardiac arrest on hospital day 3 with return of spontaneous circulation. After our long discussion with family concerning patient's poor prognosis, they decided to withdraw vasopressor support and the patient expired soon after. Soluble interleukin-

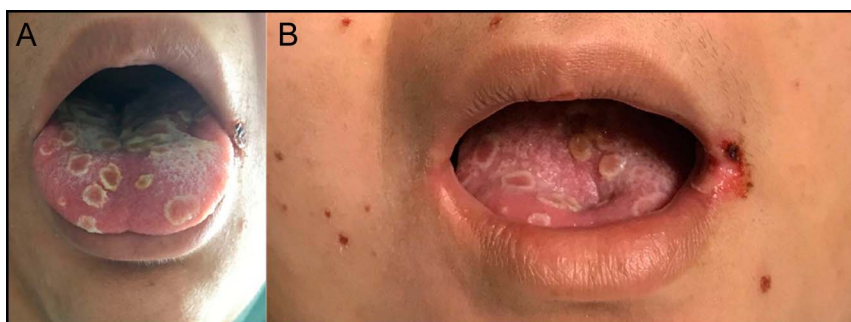
2 receptor (sIL-2R) returned as 5,820 pg/mL. Based on laboratory values and constellation of clinical findings, the patient met diagnostic criteria for HLH in the context of disseminated HSV.

## DISCUSSION

HLH is often diagnosed by having one of the genetic mutations associated with the disease or meeting 5 out of 8 diagnostic criteria: (i) fever, (ii) splenomegaly, (iii) cytopenias affecting 2 or more cell lines, (iv) serum ferritin  $> 500$  (g/L), (v) hypofibrinogenemia (fibrinogen  $< 150$  mg/dL), and/or hypertriglyceridemia ( $> 265$  mg/dL), (vi) soluble IL-2 (CD25) receptor  $> 2,400$  U/mL, (vii) hemophagocytosis (in biopsy samples of bone marrow, spleen, or lymph nodes), and (viii) low or absent natural killer cell activity.

Our patient met at least 6 out of the 8 above criteria, although biopsy could not be obtained given patient's rapid decompensation and family's decline of autopsy. Natural killer cell function testing was not ordered as this test is not widely available and more useful in diagnosing familial HLH. There have only been a few case reports of HLH secondary to HSV infection, and most occurrences are seen in neonates. It is likely in this case that the HSV caused a cytokine reaction leading to unregulated production and activation of macrophages, histiocytes, and T cells. Usually, disseminated HSV occurs in immunocompromised patients, unlike our patient who was previously healthy and had no known primary or secondary immunodeficiency disorders.<sup>3–6</sup> However, it is possible that undetected natural killer cell deficiencies may lead to increased susceptibility to HSV if the defect lies in secretory granule, secretion, or granule contents, as seen in the hemophagocytic disorders.

HLH and ALF may have overlapping diagnostic features as most cases of HLH present with some degree of hepatitis and coagulopathy.<sup>7</sup> To further complicate the situation, elevated CD25 (also known as sIL-2R) and hyperferritinemia can be seen in both conditions. In a study by Muller et al, serum levels of sIL-2R were found to be significantly elevated in acute viral hepatitis during the first week of disease onset, in the range of  $1,319 \pm 527$  units/mL.<sup>8</sup> To help differentiate between HLH and



**Figure 2.** Photographs of (A) patient's tongue showing ulcerating lesions, likely herpes simplex virus, and (B) patient's mouth, showing ulcerated and crusted lesions.

ALF, a serum sIL-2R level  $>2,500$  U/mL has been shown to be 100% sensitive and 72.5% specific for HLH. The specificity increases to 93% as the level reaches above 10,000 U/mL.<sup>9</sup> In HLH, hyperferritinemia is attributed to activated macrophages that act as the driving force behind the inflammatory immune response, whereas the hyperferritinemia seen in ALF has been attributed to hepatic necrosis. In patients with acute hepatitis including ALF, serum ferritin concentrations were found to be positively correlated with the level of ALT. This correlation was even more pronounced in cases of viral hepatitis.<sup>10</sup> It has been proposed that macrophage overactivation may play a role in the development of ALF as marked by increased macrophage byproducts, such as CD-163 and osteopontin, detected in the serum of these patients.<sup>11,12</sup> These findings suggest that HLH and acute hepatitis may share a common pathway in terms of pathogenesis and macrophage activation.

Based on the aforementioned data, ferritin level  $>40,000$  ng/mL and sIL-2R  $> 5,000$  U/mL were out of proportion to simple ALF and highly suggestive of HLH, although this could not be confirmed by liver or bone marrow biopsy. Additionally, it would be extremely unusual for the patient to develop disseminated HSV without an immunological trigger. Nonetheless, the differentiation between the 2 diseases is crucial as the risk of immunosuppressive therapy would be devastating in the setting of disseminated infection. In prior case reports of HSV-induced HLH, prompt treatment with intravenous acyclovir and methylprednisolone pulse therapy have shown successful outcomes.<sup>3</sup>

Lastly, the presentation of our patient in regards to HSV infection was also unusual. HSV-1 tends to present with blisters on the lips, referred to as cold sores, whereas HSV-2 typically manifests as genital lesions. However, the pattern of involvement pertaining to each subtype is not mutually exclusive. On external examination, our patient only had one lesion in her gluteal fold while the predominant ulcerative lesions affected her face, lips, and oral cavity. It is possible that she had intravaginal lesions that had not been observed as pelvic examination was not performed. Serum IgG HSV-2 and polymerase chain reaction swab for HSV-2 returned positive consistent with viral reactivation of HSV rather than a primary infection. This was reportedly the patient's first clinical episode of acute herpes, and it was likely that viral reactivation occurred in the presence of immunogenic predisposition.<sup>13</sup> In the majority of cases, severe first episodes are more likely to occur during true primary infections, in which the individual has never been previously exposed to either subtype.

## DISCLOSURES

**Author contributions:** All authors wrote the manuscript. M. Schwartz is the article guarantor.

**Financial disclosure:** None to report.

**Informed consent** could not be obtained from the family of the deceased. All identifying information has been removed from this case report to protect patient privacy.

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