Disseminated Herpes Simplex Masquerading as Hemophagocytic Lymphohistiocytosis: A Case Report

Jean W Liew, MD; Brian L Jones, MD, PhD; Alan J Hunter, MD

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INTRODUCTION

Marked elevation in serum ferritin levels may be seen in disseminated infection or severe organ failure states, but it is also present in hemophagocytic lymphohistiocytosis (HLH). Herpes simplex virus (HSV) hepatitis has a high mortality rate, even in immunocompetent individuals, in whom it is rarely reported. We present a case of hyperferritinemia with features initially suggestive of a diagnosis of HLH but that ultimately proved to be fulminant HSV hepatitis.

CASE PRESENTATION

A 56-year-old man with an indolent undiagnosed brain mass presented with progressive neurologic deficits and was found to have fevers, cytopenias, transaminitis, and hyperferritinemia. Initially, HLH was suspected; however, the ultimate diagnosis was HSV hepatitis with dissemination. Although the patient was treated with intravenous acyclovir, multiorgan failure developed, and he died.

DISCUSSION

This case highlights the importance of considering alternative causes for a rise in ferritin levels when HLH is on the differential. Additionally, we discuss the diagnostic and therapeutic implications of HSV hepatitis, and we review the literature for cases presenting in immunocompetent hosts.
HIV, cytomegalovirus, and hepatitis A, B, C, D, and E viruses. Epstein–Barr virus serostatus was consistent with prior infection without evidence of reactivation. On hospital day 3, a serum polymerase chain reaction for herpes simplex virus 2 (HSV-2) returned positive. Concurrently, a new facial rash was noted, consisting of innumerable 1- to 2-mm erythematous and hemorrhagic papules, pustules, and vesicles (Figure 1). Given the suspicion for disseminated HSV, intravenous acyclovir therapy, 10 mg/kg every 8 hours, was started. Results of the bone marrow biopsy showed no evidence of hemophagocytosis. A transjugular liver biopsy specimen revealed pathologic findings consistent with HSV hepatitis, with multifocal hepatocyte necrosis with minimal inflammation. An immunohistochemical stain was positive for HSV but negative for varicella zoster virus, cytomegalovirus, and Epstein–Barr virus.

Follow-up and Outcomes
The patient experienced progressive encephalopathy, acute renal failure, and worsening coagulopathy. He was initially given hemodialysis. However, with ongoing encephalopathy and clinical decline, after a discussion with his family, he was transitioned to comfort care measures on hospital day 5. He died 24 hours later. Figure 2 shows a timeline of the case.

His autopsy confirmed the hepatic findings of disseminated HSV infection. There was also evidence of HSV involvement in the lung and the adrenal glands. There was focal corticomedullary necrosis of the adrenal glands, with positive immunohistochemical staining for HSV. Neuropathology revealed a high-grade infiltrating astrocytoma of the cerebral white matter on the right side. Consent to publish was obtained from the patient’s family after his death. Institutional review board approval was not required.

DISCUSSION
This case of fatal, disseminated HSV in the face of a known brain lesion challenged the physicians’ diagnostic and therapeutic decision making, given that the strategies for treating HLH and disseminated HSV are diametrically opposed. Empiric immunosuppressive treatment of HLH would have worsened the HSV infection, and treatment of HSV would have had no impact on HLH. Yet, at presentation, both disorders could have presented similarly, with hyperferritinemia, cytopenias, and progressive multigland dysfunction.

HLH is a syndrome of immune dysregulation with cytokine storm and the proliferation and activation of macrophages, and should be suspected in cases of major liver dysfunction, cytopenias, coagulopathy, fevers, and evidence of systemic inflammation. The 2004 diagnostic criteria for HLH (see Sidebar: 2004 Diagnostic Criteria for Hemophagocytic Lymphohistiocytosis) include 5 of the following 8 features: Fever, splenomegaly, cytopenia in at least 2 cell lines, hypertriglyceridemia or hypofibrinogenemia, hyperferritinemia, elevated soluble interleukin-2 receptor, decreased or absent natural killer cell activity, and evidence of hemophagocytosis in bone marrow, cerebrospinal fluid, or lymph nodes. Our patient met only 3 of these criteria; we were unable to obtain testing for soluble interleukin-2 receptor or natural killer cell activity before his death. Additionally, there was no evidence of hemophagocytosis on either bone marrow, liver biopsy; however, this finding is also neither sensitive nor specific for HLH in adults. Primary HLH is caused by genetic and hereditary defects, whereas secondary HLH may be related to malignancy, autoimmune disorders, or infections. Viral-associated HLH is most commonly caused by Epstein–Barr virus, which carries a high mortality, but has rarely been associated with HSV. There are 5 previously reported cases of HSV hepatitis complicated by HLH (Table 2). In 1 case, HSV-2 was implicated; in another, the patient was found to have reactivation of both HSV-1 and HSV-2. In these cases, ferritin values ranged from 7000 to 200,000 ng/mL. The

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<th>Table 1. Laboratory values during hospital course</th>
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<tr>
<td>Laboratory value</td>
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<td>White blood cells, × 10⁹/µL</td>
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<td>Hemoglobin, g/dL</td>
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<tr>
<td>Hematocrit, %</td>
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<td>Platelets, × 10⁹/µL</td>
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<td>Sodium, mmol/L</td>
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<td>Potassium, mmol/L</td>
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<td>Chloride, mmol/L</td>
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<td>Bicarbonate, mmol/L</td>
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<td>Serum urea nitrogen, mg/dL</td>
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<td>Serum creatinine, mg/dL</td>
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<td>AST, U/L</td>
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<td>ALT, U/L</td>
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<td>ALP, IU/L</td>
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<td>Total bilirubin, mg/dL</td>
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<td>Ferritin, ng/dL</td>
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<td>Triglyceride, mg/dL</td>
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* Blank cell indicates laboratory study was not performed.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; HD = hospital day.
overall mortality was 40% although only 2 of the patients described were treated for HLH with chemotherapeutic agents.7–11 The differential diagnosis of marked hyperferritinemia is often considered limited to HLH and adult-onset Still disease, an autoinflammatory disorder whose diagnosis requires the exclusion of infectious, malignant, and autoimmune conditions. However, a retrospective analysis in adults identified that a ferritin greater than 50,000 ng/mL may also be found in individuals with renal failure, marked hepatocellular damage, infection, as well as HLH.12 Consequently, an extremely elevated ferritin level is not specific for HLH in adults. In the end, our patient’s elevated ferritin level was likely related to his disseminated HSV and resultant hepatic necrosis, with contribution from his renal failure.

Hepatitis caused by HSV infection is rare, accounting for about 1% of cases of acute liver failure in adults.2 It may be part of disseminated disease and can be caused by a primary infection or reactivation of either HSV-1 or HSV-2.14 Fulminant liver failure is associated with high mortality. HSV hepatitis and dissemination are more common in immunocompromised individuals, such as transplant recipients, patients receiving long-term corticosteroid therapy, and individuals with burns. Pregnant women and neonates also account for a large number of cases. Immunocompetent, nonpregnant adults account for 21% to 24% of all patients in prior case reports.1,14,15 In our patient, who was otherwise immunocompetent, the course of glucocorticoid therapy for his brain lesion probably was the inciting factor for his HSV infection. Common clinical manifestations and laboratory findings include fever (82–98%), leukopenia (71%), thrombocytopenia (94%), coagulopathy (35–90%), and elevated transaminases levels without cholestasis (anicteric hepatitis).1,14,16 There may also be concomitant acute renal failure in 65%.1 Mucocutaneous findings of herpetic infection range from 44% to 80% in literature reviews1,14–16; they are not a sensitive finding. Diagnosis is best accomplished with polymerase chain reaction for HSV DNA.1,15 Liver biopsy is the gold standard, with findings of confluent hemorrhagic necrosis of liver parenchyma, and ground-glass intranuclear inclusions consistent with viral cytopathic effect.14–17

The mortality from HSV hepatitis, even in immunocompetent individuals, is high. In a 1986 literature review, the mortality was greater than 80%,13 which was again demonstrated in a 1997 review.15 Norvell et al1, in 2007, found an overall 74% mortality for all cases of HSV hepatitis reported since 1969. Additionally, it

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**2004 Diagnostic Criteria for Hemophagocytic Lymphohistiocytosis**

**Fulfilment of either 1) or 2):**

1. A molecular diagnosis consistent with hemophagocytic lymphohistiocytosis is made

2. 5 of the 8 diagnostic criteria are fulfilled:
   - Fever
   - Splenomegaly
   - Cytopenias affecting ≥ 2 cell lineages in the peripheral blood
     - Hemoglobin < 9 g/dL
     - Platelets < 100 × 10^3/mL
     - Neutrophils < 1 × 10^3/mL
   - Hypertriglyceridemia and/or hypofibrinogenemia
     - Fasting triglyceride > 265 mg/dL
     - Fibrinogen < 150 mg/dL
   - Hyperferritinemia ≥ 500 ng/L
   - Hemophagocytosis in bone marrow, spleen, or lymph nodes
   - Low or absent natural killer cell activity
   - Soluble CD25 (interleukin-2 receptor)
is sobering to note that mortality remains approximately 50% even for those treated with acyclovir. A 1997 review of patients with HSV hepatitis noted that only 28% of patients received antiviral agents, yet by 2007, this rate had increased to only 37%.

**CONCLUSION**

The clinical spectrum of an acute inflammatory febrile syndrome associated with marked hepatic dysfunction, cytopenias, coagulopathy, and hyperferritinemia should prompt diagnostic consideration of not only HLH but other causes as well. Hyperferritinemia in the setting of multiorgan dysfunction or failure is a known association with HLH, but it may be seen in other inflammatory and infectious processes. Such diagnoses must be excluded before the treatment of HLH, because this treatment may have deleterious effects if the diagnosis is incorrect. In our patient, the ultimately diagnosed disseminated HSV, likely triggered by high-dose corticosteroid treatment for mass-associated brain edema, was the cause of death. HSV hepatitis has a high mortality rate, even in immunocompetent individuals, in whom it is rarely reported. One must have a high index of suspicion for this diagnosis because cutaneous lesions are not always present. The early use of acyclovir may improve outcomes, although it did not alter the course in our patient.

**Disclosure Statement**

The author(s) have no conflicts of interest to disclose.

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**How to Cite this Article**


**References**

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