Stevens-Johnson syndrome complicated by fatal hemophagocytic lymphohistiocytosis

Nathan Vengalil, BA,[a] Mio Nakamura, MD, MS,[b] Kiyanna Williams, MD,[b] and Milad Eshaq, MD[b]
Ann Arbor, Michigan

Key words: drug eruption; hemophagocytic lymphohistiocytosis; Stevens-Johnson syndrome; toxic epidermal necrolysis.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening disorder characterized by multi-organ failure due to uncontrolled activation of cytotoxic T-lymphocytes and natural killer (NK) cells. Here, we describe a rare and difficult case of Stevens-Johnson syndrome (SJS) complicated by HLH.

Abbreviations used:

EBV: Epstein-Barr virus
HLH: hemophagocytic lymphohistiocytosis
NK: natural killer
SJS: Stevens-Johnson syndrome
TEN: toxic epidermal necrolysis

CASE REPORT

A 26-year-old previously healthy man was transferred from an outside hospital with rapidly worsening rash, fever, and elevated liver function test results with aspartate aminotransferase of 10,000 IU/L and alanine aminotransferase of 14,000 IU/L. The patient had traveled to India 2 months prior and on return developed undulating fever and mild congestion. He was prescribed amoxicillin and acetaminophen with initial improvement for 2 weeks but again developed fever. He took nonsteroidal anti-inflammatory drugs and acetaminophen without relief. He was prescribed another course of amoxicillin, as well as oral corticosteroids, 7 days before his presentation.

On examination, the patient was febrile and uncomfortable but was otherwise stable. He had erosions on the upper and lower lips with hemorrhagic and yellow crust. Violaceous to dusky red macules, papules, and plaques, and vesicles and bullae with positive Nikolsky sign were scattered over the face, ears, trunk, and lateral aspect of the upper arms. Several erythematous macules were noted on the bilateral palms and soles. Left-sided cervical lymphadenopathy was noted. Differential diagnosis included SJS and drug rash with eosinophilia and systemic symptoms, most likely due to amoxicillin or nonsteroidal anti-inflammatory drugs, and infectious etiologies. Autoimmune blistering conditions were considered but would not explain the elevated liver function test results. Punch biopsies for H&E and direct immunofluorescence showed subepidermal bullae with full-thickness epidermal necrosis and a negative result on direct immunofluorescence, consistent with SJS. The patient was transferred to the burn unit and given intravenous dexamethasone.

The patient's condition continued to deteriorate, with evidence of worsening liver failure and new-onset acute kidney injury and coagulopathy. Multiple specialties were consulted, including hepatology, nephrology, infectious disease, rheumatology, and hematology. Infectious disease workup results, including for studies for HIV, cytomegalovirus, Epstein-Barr virus (EBV), malaria, rickettsial diseases, human herpesvirus-6, toxoplasmosis, rubella, rubeola, and spirochetes, were negative. Autoimmune workup showed negative anti-nuclear antibodies and extractable nuclear antigen panel. Soluble interleukin 2 receptor levels were elevated. Bone marrow aspiration showed hemophagocytosis.

From the University of Michigan Medical School[a] and Department of Dermatology, University of Michigan Medical School.[b]
Funding sources: None.
Conflicts of interest: None disclosed.
Correspondence to: Mio Nakamura, MD, MS, Department of Dermatology, University of Michigan, 1910 Taubman Center, 1500 E Medical Center Dr, Ann Arbor, MI 48109. E-mail: mionak@med.umich.edu.

JAAD Case Reports 2019;5:857-60.
2352-5126

https://doi.org/10.1016/j.jdcr.2019.07.022

The patient met the criteria for HLH, including fevers, splenomegaly, elevated ferritin, hypofibrinogenemia, and hemophagocytosis in the bone marrow. The patient began receiving intravenous ruxolitinib.

Over the hospital course, the patient's desquamating rash progressively worsened, complicated by a pseudomonal infection of his back wounds. The patient continued to deteriorate with progressive multiorgan failure. He developed cerebral edema and died on hospital day 11.

DISCUSSION

HLH, also known as hemophagocytic syndrome, is a life-threatening disorder caused by uncontrolled activation of cytotoxic T-lymphocytes and NK cells, resulting in an immune-mediated destruction of various organ systems. Until recently, HLH was considered a pediatric disorder; however, HLH can affect patients of any age, with adults comprising approximately 40% of cases. HLH is a rare disease, estimated to affect 1 to 225 per 300,00 live births and 1 of 2000 adult admissions at tertiary medical centers.[1]

HLH is classified as either primary (familial) or secondary (reactive). Primary HLH shows an autosomal recessive inheritance pattern, and the associated genetic mutations alter the release of cytolytic granules from $CD8^+$ cytotoxic T cells and NK cells, rendering both insufficient at destroying immune-activating stimuli and leading to overactivation of macrophages and hemophagocytosis, tissue destruction, and organ failure. Secondary HLH may result from malignancy, infection, or autoimmune stimuli without a contributing genetic defect. An aberrant pattern of T-lymphocyte activation and differentiation has been observed. Of note, macrophage activation syndrome is a subtype of HLH that occurs in the background of autoimmune disease.[1]

The clinical presentation of HLH is nonspecific. The HLH-2004 diagnostic criteria are shown in Table I. Treatment of HLH includes identifying and removing potential triggers and chemoimmunotherapy consisting of etoposide (VP-16) and dexamethasone, with intrathecal methotrexate if central nervous system involvement occurs. If the disease is resistant to initial treatment, bone marrow transplantation can be considered.[2] Recently, there have been reports of successful treatment of HLH using ruxolitinib.[1] HLH has a poor prognosis, especially in adults, and is fatal if left untreated.[2]

SJS/toxic epidermal necrolysis (TEN) may be associated with HLH. To date, there have been 8 published cases of SJS/TEN complicated by HLH (Table II).[3-10] The pathogenesis of this possible association is unknown. In SJS/TEN, analysis of blister fluid shows interferon gamma as the predominant cytokine. Likewise, interferon gamma may be the major mediator of macrophage activation in HLH induced by infection.[10] Both processes involve increased circulating $CD8^+$ T cells; in HLH, $CD8^+$ T cells are unable to be downregulated, whereas in SJS/TEN they are inappropriately activated, leading to keratinocyte apoptosis.[3]

The clinical picture of SJS/TEN alone and SJS/TEN in combination with HLH are extremely similar. Although extensive skin involvement is more characteristic of SJS/TEN, multisystem organ dysfunction can occur in both SJS/TEN and HLH.[3] Both disease processes also share common triggers, including drugs and infection. As a result, it can be extremely challenging for a clinician to suspect HLH in the setting of SJS/TEN.

Recently, clinical markers have been identified to help clinicians consider HLH in the setting of SJS/TEN, the most important being pancytopenia. Easily detected on routine complete blood count, cytopenia in 2 or more cell lineages is the most common laboratory result in HLH and is very uncommon in SJS. Other markers to consider include hyperferritinemia because a ferritin level over 10,000 ng/mL has been shown to be 90% sensitive and 96% specific for

Table I. Diagnostic criteria based on HLH-2004 guidelines[2,3]

Diagnosis can be made if either of the following conditions are met:

A molecular diagnosis is consistent with HLH: pathologic mutations in PRF1, UNC13D, STX11, SH2D1A, BIRC4, Munc18-2, or Rab27a

OR

At least 5 out of the 8 clinical criteria listed below are met:

1. Fever $\geq$ 38.5°C
2. Splenomegaly
3. Cytopenias (affecting $\geq$ 2 lineages)
   a. Hemoglobin level $<$ 90 g/L (infants $<$4 weeks: $<$100 g/L)
   b. Platelet count $<$ 100 $\times$ 10^9/L
   c. Neutrophil count $<$ 1 $\times$ 10^9/L
4. Hypertriglyceridemia (fasting, $\geq$3 mmol/L) and/or hypofibrinogenemia ($<$1.5 g/L)
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver with no evidence of malignancy
6. Low or absent NK cell activity
7. Ferritin $\geq$ 500 ng/mL
8. Soluble CD25 (soluble IL-2 receptor) level $\geq$ 2400 U/mL

HLH, Hemophagocytic lymphohistiocytosis; *IL*, interleukin; *NK*, natural killer.

Table II. Documented cases of SJS/TEN complicated by HLH

Patient	Suspected trigger	Pertinent history	Treatment of HLH	Outcome
Pediatric				
7-month-old boy[4]	Ceftriaxone sodium	Bronchitis	Cyclosporine A, methylprednisolone	Discharged healthy on day 25
17-month-old boy[3]	Dicloxacillin, cephalexin, ibuprofen	Test results for laryngotracheitis, HHV-6, parainfluenza, and rhinovirus positive	Etoposide, dexamethasone	Fully recovered after 2 months
2-year-old girl[5]	EBV infection	Received IVIG, aspirin, flucloxacillin, gentamicin, and clindamycin	Steroids, methotrexate, etoposide, rituximab	After bone marrow transplant, healthy 8 months later
4-year-old boy[6]	Cephalosporin, ibuprofen	URI	High-dose IVIG, methylprednisolone	Discharged healthy
12-year-old boy[7]	Meropenem, vancomycin, sodium valproate	On dialysis, contracted MRSA	GM-CSF, blood transfusions	Died of sepsis and renal failure
16-year-old girl[8]	EBV infection	EBV-infected $CD8^+$ T lymphocytes on skin biopsy	Etoposide and dexamethasone	Improved with mild residual erythema and desquamation of skin
Adult				
34-year-old woman[9]	Antidepressants	Parvovirus-B19 infection	High-dose γ-globulin and plasmapheresis	Developed MRSA infection and DIC and died of brain hemorrhage
76-year-old woman[10]	Etodolac	N/A	N/A	Died due to sepsis and hepatic failure

DIC, Disseminated intravascular coagulation; *EBV*, Epstein-Barr virus; *HHV-6*, human herpesvirus 6; *HLH*, hemophagocytic lymphohistiocytosis; *IVIG*, intravenous immunoglobulin; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *N/A*, not applicable; *SJS/TEN*, Stevens-Johnson syndrome/toxic epidermal necrolysis; *URI*, upper respiratory infection.

HLH in children. Hemophagocytosis is also important to consider, but it is 83% sensitive and only 60% specific for HLH; furthermore, hemophagocytosis may not be present early at the onset of HLH.[6] Early detection of HLH is crucial to decrease the morbidity and mortality of this life-threatening condition.

REFERENCES

1. Al-Samkari H, Berliner N. Hemophagocytic lymphohistiocytosis. *Annu Rev Pathol*. 2018;13:27-49.
2. Henter J-I, Horne A, Aricó M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48(2):124-131.
3. Sniderman JDS, Cuvelier GDE, Veroukis S, Hansen G. Toxic epidermal necrolysis and hemophagocytic lymphohistiocytosis: a case report and literature review. *Clin Case Rep*. 2015;3(2):121-125.
4. Zeng H, Chen X. First case report of Stevens-Johnson syndrome complicated with macrophage activation syndrome. *Rheumatol Rep*. 2009;1(1):e9.
5. Sharma N, Clark J, Pham H, et al. TEN-like eruption in setting of EBV positive T-cell lymphoproliferative disease with HLH, in a child: TEN-like eruption in EBV disease & HLH. *Australas J Dermatol*. 2014;55(3):e44-e47.
6. Fan Z-D, Qian X-Q, Yu H-G. Pancytopenia as an early indicator for Stevens-Johnson syndrome complicated with hemophagocytic lymphohistiocytosis: a case report. *BMC Pediatr*. 2014;14:38.
7. Pakran J, Pavithran K, Kuruvila S, Anand M. Coexistence of Stevens-Johnson syndrome and hemophagocytic syndrome. *Indian J Pediatr Dermatol*. 2013;14(3):83.
8. Kawachi Y, Itoh M, Fujisawa Y, et al. Epidermal cell necrosis with direct epidermal infiltration of Epstein-Barr virus (EBV)-encoded small nuclear RNA-positive T lymphocytes in a patient with EBV-associated haemophagocytic syndrome. *Br J Dermatol*. 2007;157(5):1053-1056.
9. Matsumoto Y, Naniwa D, Banno S, Sugiura Y. The efficacy of therapeutic plasmapheresis for the treatment of fatal hemophagocytic syndrome: two case reports. *Ther Apher*. 1998;2(4):300-304.
10. Yamaoka T, Azukizawa H, Tanemura A, et al. Toxic epidermal necrolysis complicated by sepsis, haemophagocytic syndrome, and severe liver dysfunction associated with elevated interleukin-10 production. *Eur J Dermatol*. 2012;22(6):815-817.