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CASE REPORT

Toxic epidermal necrolysis and hemophagocytic lymphohistiocytosis: a case report and literature review

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Key Clinical Message

Diagnostic criteria for hemophagocytic lymphohistiocytosis should be reviewed early in critically ill patients with toxic epidermal necrolysis, multisystem dysfunction, and a deteriorating clinical trajectory.

Keywords

Critical illness, hemophagocytic lymphohistiocytosis, toxic epidermal necrolysis.

Introduction

Toxic epidermal necrolysis (TEN) is a life-threatening mucocutaneous disease characterized by extensive epidermal sloughing complicated by multisystem organ dysfunction [1]. TEN is mediated by activated CD8+ T cells that induce keratinocyte apoptosis [1] and is most commonly attributed to drugs, such as sulfonamides, anticonvulsants, penicillin and nonsteroidal anti-inflammatory medications [2].

By comparison, hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory syndrome characterized by fevers, cytopenias, splenomegaly, decreased NK cell function, and biochemical features of excessive inflammation (Table 1). T-lymphocytes and macrophages are inappropriately activated in HLH, resulting in hemophagocytosis of blood cells in the bone marrow, widespread tissue infiltration by histiocytes, excessive cytokine release, and life-threatening multi-system organ dysfunction [3]. Although an extensive list of infectious agents, malignancies, rheumatologic and genetic conditions are associated with the development of HLH many cases have no identified trigger or confirmed genetic etiology.

Although cutaneous maculopapular rashes are described in HLH [4–9], extensive epidermal desquamative lesions are rare with only seven published cases to date (Table 2). We present a pediatric case of TEN in association with HLH, and review the literature. An increased awareness of this association is necessary, ensuring the diagnosis of HLH is considered early and urgent life-saving chemotherapy initiated.

Case

A previously healthy 17-month-old boy was hospitalized for severe laryngotracheitis, requiring 7 days of ventilatory support. Endotracheal cultures grew methicillin-sensitive *Staphylococcus aureus*, and nasopharyngeal aspirates positive for both parainfluenza 1 virus and rhinovirus. The patient was treated with IV cloxacillin and 5 days of dexamethasone, before being discharged home on oral cephalexin and ibuprofen.

Nine days after discharge the patient presented to the emergency department with a 5-day history of a spreading erythematous rash (Fig. 1A) and 3 days of high fevers. Examination revealed a toxic, febrile and drooling toddler, with an extensive maculopapular rash, oral mucositis and biphasic stridor. Hepatosplenomegaly was not initially present. Computed tomography scanning demon-

Table 1. Diagnostic criteria for hemophagocytic lymphohistiocytosis (adapted [10], with units converted to SI units).

A. Molecular diagnosis consistent with HLH: pathologic mutations of PRF1, UNC13D, Munc18-2, Rab27a, STX11, SH2D1A, or BIRC4
Or
B. Five of the eight criteria listed below being fulfilled:
1. Fever ≥38.5°C
2. Splenomegaly
3. Cytopenias (affecting at least 2 of 3 lineages in the peripheral blood)
Hemoglobin <90 g/L (in infants <4 weeks: <100 g/L)
Platelets $<100 \times 10^9$/L
Neutrophils $<1 \times 10^9$/L
4. Hypertriglyceridemia (fasting, ≥3 mmol/L) and/or hypofibrinogenemia (<1.5 g/L).
5. Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver
6. Low or Absent NK cell activity
7. Ferritin ≥500 μg/L (most cases are >3000 μg/L; with >10000 μg/L being highly suspicious for HLH).
8. Elevated soluble IL-2 receptor alpha (sCD25) >2 standard deviations from the mean for age and institution-specific normative lab values.

HLH, hemophagocytic lymphohistiocytosis.

strated significant narrowing of the trachea and extensive lymphadenopathy throughout the neck. Laboratory investigation revealed increased aspartate aminotransferase (1179 U/L), alanine aminotransferase (1042 U/L), and lactate dehydrogenase (1203 U/L) levels, but normal total and direct bilirubin (6 and 5 μmol/L), gamma-glutamyl transferase (60 U/L) and alkaline phosphatase (143 U/L). Initial complete blood count revealed a normal total white blood cell count (8.7×10^9/L), normal neutrophil count (6.13×10^9/L), normal platelet count (161×10^9/L), and a mild normochromic normocytic anemia (hemoglobin 108 g/L). Cefotaxime, vancomycin, acyclovir, and high-dose methylprednisolone (4 mg/kg per day) were initiated and reintubation was required for airway protection.

Over the next week the rash evolved, progressing to full desquamation of most of the patient's body surface area. Skin biopsy confirmed the clinical diagnosis of TEN (Fig. 1B) and intravenous immunoglobulin was initiated. Either ibuprofen or cephalexin was felt to be initiating factors for the TEN. During this time, the clinical status of the patient deteriorated, with development of significant fluid third spacing, acute respiratory distress syndrome requiring increased ventilator settings, cardiovascular shock requiring inotropes and vasopressors, and a direct hyperbilirubinemia. Pancytopenia, coagulopathy and bleeding ensued, and was managed with red blood cell, plasma and platelet transfusions. Persistent temperature spikes above 38.5°C continued for 12 days after readmission to hospital.

During the progression of critical illness, all eight diagnostic criteria for HLH were met [10] despite corticosteroid use for airway edema and refractory shock. These included persistent fevers ≥38.5°C, splenomegaly, cytopenias affecting all major cell lineages (lowest platelet count of 12×10^9/L, lowest hemoglobin 75 g/L, lowest neutrophil count 0.02×10^9/L), hypertriglyceridemia (4.3 mmol/L), and hypofibrinogenemia (0.9 g/L), unequivocal and extensive hemophagocytosis in a bone marrow aspirate (Fig. 1C), absent natural killer cell activity, hyperferritinemia (7107 μg/L; normal 20–140), and elevated soluble IL2-receptor-alpha levels (16,636 U/L; normal 334–3026 U/L). A lumbar puncture revealed no evidence of hemophagocytosis in the cerebrospinal fluid.

An extensive infectious disease evaluation revealed only the presence of human herpes virus-6 PCR positivity (3000 viral copies/mL) in the bone marrow aspirate and *Candida albicans* by culture from an indwelling urinary catheter. Multiple culture, serology, and PCR tests from the blood, CSF, nasopharynx, mouth, and stool for Epstein–Barr Virus (EBV), Cytomegalovirus, Herpes Simplex Virus-1 and -2, Adenovirus, Varicella virus,

Table 2. Summary of reported cases of desquamative conditions and HLH.

References	Age (yr)	Sex	Mucocutaneous reaction	Potential medication trigger	HLH disease association	Outcome
Kawachi et al. [11]	16	F	SJS/TEN	None identified	EBV	Discharged home. Small areas of erythema and desquamation.
Zeng and Chen [18]	7 months	M	SJS	Ceftriaxone	Unknown	Discharged home in good health
Sharma et al. [17]	2	F	TEN	None identified	EBV	One relapse, no permanent skin damage or developmental delay
Pakran et al. [19]	12	F	SJS/TEN	Sodium valproate Vancomycin	MRSA	Died on day 8. Was on dialysis, awaiting renal transplantation.
Fan et al. [12]	4	M	SJS	Ibuprofen Cephalosporin	Unknown	Discharged home in good condition
Mastumoto et al. [16]	34	F	SJS	Antidepressants	HPV-B19	Died due to MRSA sepsis and DIC.
Yamaoka et al. [13]	76	F	TEN	Etodolac?	Unknown	Died due to sepsis and hepatic dysfunction.

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; EBV, Epstein–Barr virus.

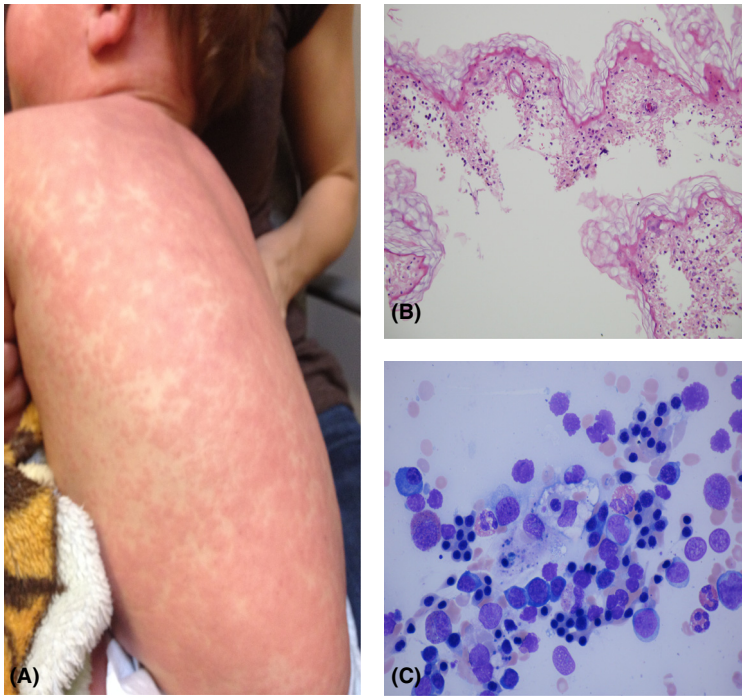

Figure 1. (A) Evolving maculopapular rash prior to desquamation; (B) Upper chest skin biopsy showing completely detached epidermis and full epidermal necrosis; (C) Bone marrow aspirate demonstrating monocytes engulfing red blood cell precursors. (Giemsa stain).

Enteroviruses, common respiratory viral pathogens, bacterial and fungal cultures were negative.

Further HLH evaluation revealed normal perforin, granzyme, SLAM-associated protein (SAP), and X-linked inhibitor of apoptosis protein (XIAP) expression by flow cytometry. A CD107a mobilization assay was also normal (mean cell fluorescence 215; normal 207–678), making genetic degranulation disorders associated with HLH less likely.

Emergent chemotherapy was initiated with etoposide and dexamethasone according to the HLH-94 protocol [10], and continued for 8 weeks. The patient made a full recovery over the next 2-months, with resolution of TEN and normalization of biochemical and hematologic parameters of HLH. No HLH genetic mutation, including mutations in UNC13D, STX11, RAB27A, and STXBP2 were found. PRF1, LYST, and x-linked lymphoproliferative disorder mutations in SH2D1A and XIAP were not performed due to normal perforin levels, absence of Chediak-Higashi features, and normal SAP and XIAP levels, respectively. Six months after initial diagnosis, there has been no recurrence of either the TEN or HLH.

Discussion

We report a case of HLH in association with TEN. A definitive etiology for either disorder could not be determined, although we suspect that ibuprofen or cephalexin may have played a role. Alternatively, we cannot discount that an infectious agent (*S. aureus*, parainfluenza virus, rhinovirus, or HHV-6) triggered the process. Regardless, this case illustrates that the severe, life-threatening syndrome of HLH can occur in the context of TEN, and the two disorders should not be considered mutually exclusive. Healthcare providers involved in the diagnosis and management of TEN must be aware of the possibility of concomitant HLH, particularly in cases with severe multi-organ system involvement.

Membranous desquamation prior to HLH diagnosis has been documented in case reports [11–13]. This may be a spurious observation, or herald a pivotable aspect of disease progression. Both TEN and HLH overlap in the defective activation of cytotoxic CD8+ lymphocytes and elevation of serum granulysin [14, 15]. This relation may suggest that a common process could account for both presentations. Our case describes a boy with a confirmed viral and bacterial prodrome, followed by a presumptive immune drug response. A two-hit hypothesis has support in three other cases [12, 13, 16], whereby nonspecific viral upper respiratory tract symptoms temporally overlapped with medications commonly implicated with TEN. Two other TEN cases [11, 17] reported no mucosal involvement and isolated EBV from the skin lesions, suggesting a single viral entity.

Our patient's favorable outcome is consistent with other pediatric case reports [11, 12, 17, 18]. One patient relapsed [19], but was effectively managed, demonstrating the need for close surveillance. One fatality did occur, however [12], with a patient experiencing considerable comorbidities including chronic renal failure requiring hemodialysis. Considering that the overall pediatric mortality rate for TEN is below 30% [3], and for secondary HLH ranges between 8% and 22% [20], these reported outcomes are encouraging.

The possible relation between HLH and desquamative conditions presents at least two questions. First, how prevalent is undiagnosed HLH in fatal cases of TEN? In adults, Wolf et al. [21] and Rejaratnam et al. [22] reported prognostic factors for TEN mortality that included severe anemia, neutropenia, lymphopenia, and visceral organ involvement. Given the overlap with these factors and HLH diagnostic criteria, these findings may suggest the presence of underappreciated HLH. Second, what is the relation between drug-induced hypersensitivity syndrome (DIHS), severe cutaneous adverse reactions and HLH? In a prospective DIHS adult cohort [23], patients presented with a constitution of symptoms including fever, hypertriglyceridemia, hyperferritinemia, pancytopenia, subtle mucosal involvement, and erythroderma with mild desquamation. Stronger associations between DIHS and confirmed HLH without desquamation have been published with antiepileptic drugs, chemotherapy, immunomodulators, and antibiotics.

Diagnosing HLH is challenging. It requires a recognition that it often occurs in the context of more defined entities such as infection, malignancy, and apparently, TEN. It also involves processing a number of nonspecific clues (e.g., hyperferritinemia, persistent fevers, cytopenias) within the diagnostic framework for HLH (Table 1). The criteria may be variably present at different time points, and affected by concomitant corticosteroid use before a HLH diagnosis is considered. Finally, the ability to perform specialized tests (NK cell function assays, soluble IL-2 receptor levels) may not readily available, even in tertiary-care hospitals.

HLH is likely underdiagnosed due to a lack of awareness about the condition, the inability to access specialized diagnostic testing, and erroneous beliefs that the disorder is exceedingly rare and that failure to identify hemophagocytosis in bone marrow aspirates rules the condition out [10]. Our center has formalized processes, including payment, for urgent specialized testing of NK cell function and soluble IL2-receptor alpha at Cincinnati Children's Hospital's Diagnostic Immunology Laboratory (http://www.cincinnatichildrens.org/service/i/immune-deficiency/diagnostic-lab/). This, combined with early consultation to pediatric hematology-oncology, has resulted in a number of HLH diagnoses being made.

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Conflict of Interest

None declared.

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