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Hemophagocytic Lymphohistiocytosis: Overlooked in Critically Ill Adults?

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Abstract

Hemophagocytic Lymphohistiocytosis (HLH) is a clinical syndrome of excessive immune activation. Accurate and timely identification remains challenging. We present a case series of 15 adult patients diagnosed with HLH at our center. The most common triggers were malignancy and infection (specifically Epstein-Barr Virus). Overall mortality was 60%, with a median time from diagnosis to death of 37 days. There was no treatment regimen associated with better survival in our series. We suggest that treatment should be tailored to the suspected underlying etiology, and point to the need for randomized controlled trials in adults to determine the most effective treatment regimen.

Abbreviations

HLH : Hemophagocytic Lymphohistiocytosis

EBV : Epstein-Barr Virus

CMV : Cytomegalovirus

HSV : Herpes Simplex Virus

Introduction

Hemophagocytic Lymphohistiocytosis (HLH), also known as hemophagocytic syndrome, is a clinical syndrome provoked by excessive immune activation and a subsequent overwhelming inflammatory response. It is most often clinically characterized by fevers, cytopenias, and hyperferritinemia, but can also include liver dysfunction, coagulopathy, hepatosplenomegaly, lymphadenopathy, neurologic changes, hypertriglyceridemia, rashes, and renal failure. The name is derived from the finding of hemophagocytosis in the bone marrow, spleen, or liver.

There are two subtypes of HLH: primary (or familial) and secondary. Primary HLH usually occurs in children under the age of 2 years [1-2] and is linked to primary immunodeficiencies (Chediak-Higashi syndrome, Gricelli syndrome, X-linked proliferative syndrome) as well as autosomal recessive genetic defects in T-lymphocyte NK-cell function [3]. Estimates of the incidence of primary HLH range from 0.5-1/100,000 primarily in children [4]. Treatment consists of chemotherapy and immunosuppression, with allogeneic bone marrow transplant the only known cure [5]. Survival is approximately 50% at 5 years [6].

Secondary HLH occurs in patients without an underlying immune defect and is typically diagnosed in older children and adults. Known triggers include malignancy (primarily lymphomas), infection (most commonly Epstein-Barr Virus (EBV) and Cytomegalovirus (CMV), autoimmune disease (most commonly systemic lupus erythematosus), certain drugs, or rarely post-hematopoietic stem cell or solid organ transplant[4]. As the presentation is variable and nonspecific, mimicking other entities including sepsis, the diagnosis is frequently delayed and the prognosis is exceedingly poor, with mortality rates approximately 45-75% [4-9]. Here we present a case series of 15 patients diagnosed with HLH at our center, and relate our center's experience to a brief review of the literature.

Representative Cases

Case 1

A 58-year-old woman with a remote history of localized melanoma presented with several months of weakness, fatigue, anorexia, fevers, night sweats, and hearing loss. The symptoms

started after she cleaned out her son's trailer and was exposed to frogs, lizards and cat feces. She was previously active, but she became unable to walk and developed fevers, night sweats, and rapidly progressive hearing loss. She rapidly became ill and was brought to the hospital by emergency services. She was lethargic and hypothermic to 90 F. She did not take any medications and had no known allergies. Family history was notable for hemochromatosis in her father. She was a housekeeper, married, lived in a rural area and had not traveled outside the Southeastern United States.

On admission, she was tachycardic, tachypneic, somnolent and oriented only to person. Physical examination was notable for open oral lesions, a single enlarged cervical lymph node, and diffuse pulmonary rales. Laboratory studies revealed normocytic anemia, thrombocytopenia, ferritin > 15,000 ng/mL (>33,705 pmol/L), LDH 3359 U/L (56.1 ukat/L), and soluble interleukin-2 receptor of 11,020 U/mL. A peripheral blood smear showed hemophagocytosis, though relevance of this finding in the blood is unclear. CT of the abdomen and pelvis revealed a retroperitoneal soft tissue density suggestive of malignancy. MRI of the brain showed focal dural enhancement along the left frontal lobe concerning for an inflammatory or neoplastic process. A bone marrow biopsy revealed peripheral T-cell lymphoma not otherwise specified. She was started on intravenous dexamethasone with plans to initiate intrathecal methotrexate. Unfortunately, she became tachypneic and unarousable, requiring intubation. Given her poor prognosis, her family chose supportive care and she died soon thereafter.

Case 2

A 57-year-old man with hypertension and type 2 diabetes presented with two months of fatigue, loss of taste, drenching night sweats, and a 50 lb weight loss as well as two weeks of cramping lower abdominal pain, non-bloody diarrhea, and dark urine. Physical examination revealed scleral icterus, lower abdominal tenderness, and hepatosplenomegaly. Laboratory studies were notable for hyponatremia, pancytopenia, and abnormal liver function tests. CT, MRI, and MRCP of the abdomen revealed an enlarged, heterogeneous liver, splenomegaly, and ascites. There was a cystic mass in the body of the pancreas but no biliary ductal dilatation. Serum protein electrophoresis showed an asymmetric gamma peak, and monoclonal IgG lambda was detected on immunofixation. Bone marrow biopsy exam was negative for lymphoma or blasts. A liver biopsy revealed granulomatous inflammation and sinusoidal congestion suggestive of multiple concurrent processes. He was started on prednisone for presumed sarcoidosis and experienced relief of some of his symptoms. However, one week later he developed fever to 102 F and profuse diarrhea; he was found to be hypotensive and tachycardic. Infectious workup including bacterial cultures, viral hepatitis, HIV, EBV/VZV, tuberculosis, parasites, *Bartonella* and *Brucella* was negative. Autoimmune workup was unrevealing. Repeat bone marrow exam did not show hemophagocytosis. However, further studies revealed elevated ferritin to 4906 ng/mL (11,024 pmol/L) with negative hemochromatosis screening, fasting triglycerides 223 mg/dL (2.52 mmol/L), and soluble CD25 of 18,865 U/mL, consistent with HLH complicated by granulomatous hepatitis.

He was started on dexamethasone and etoposide per HLH-2004 recommendations [5]. He improved, though after several months on maintenance dexamethasone, he was admitted for severe *Clostridium difficile* colitis, and was then readmitted for fever of unknown origin. He developed progressive renal insufficiency requiring dialysis and hepatic failure despite treatment with azathioprine and high-dose intravenous steroids for granulomatous liver disease. Shortly after his second session, he developed rigors and became hypoxic, tachycardic and hypotensive, necessitating initiation of vasopressors and continuous hemodialysis. His condition continued to decline; ultimately, his family decided to pursue comfort care and he died soon thereafter.

Methods

We performed a retrospective case series of patients evaluated at our center from 2005 to 2015. Potential subjects were identified through faculty polling and a search of an ICD-9 database for the ICD-9 code 288.4, which encompasses HLH, familial HLH, and hemophagocytic syndrome. Subjects were included if they had a diagnosis of secondary HLH by HLH-2004 criteria [5], or if they were given the diagnosis in the medical record by an attending hematologist or oncologist. We chose this definition given the unknown sensitivity and specificity of HLH-2004 criteria in adults with secondary HLH, as well as the less common use of these criteria during the earlier portion of our study window. Manual chart review was used to extract clinical data.

Results

Our initial search identified 46 subjects with the specified ICD-9 code who presented to our center between 2005 and 2015. Of these, 18 met our definition of HLH. Three subjects with familial HLH were excluded, leaving 15 subjects with secondary HLH for analysis. The baseline characteristics of our subjects are shown in (Table 1).

Characteristic	Number of Patients (%)
Gender	
Male	12 (80%)
Female	3 (20%)

Age	
< 30	6 (40%)
31 - 50	3 (20%)
> 50	6 (40%)
Race	
White/Caucasian	9 (60%)
Black/African American	4 (27%)
Hispanic	2 (13%)
Precipitant of HLH	
Infection	4 (27%)
Malignancy	6 (40%)
Autoimmune/genetic disease	3 (20%)
Unclear	2 (13%)

Table 1: Baseline Characteristics.

The majority (80%) were male. Most were Caucasian, but consistent with our center's diverse patient population, 27% were African American and 13% were Hispanic. There appeared to be a bimodal age distribution, with 40% under the age of 30 and an additional 40% over the age of 50. Common precipitants for HLH included malignancy (40%), infection (27%), and autoimmune or genetic disease (20%). Two subjects did not have an identified trigger. Twelve out of 15 patients met HLH-2004 diagnostic criteria (Table 2).

Criterion	Number of Patients Meeting Out of Number Evaluated
Fever	14/15
Splenomegaly	11/15
Two peripheral blood cytopenias	12/14
Thrombocytopenia (< 150K)	14/14
Anemia	12/14
Leukopenia (<4K)	10/13
Ferritin > 500 ng/mL	14/14
CD25 > 2 SD above laboratory mean	9/9
Hemophagocytosis	7/13
Hypertriglyceridemia (> 200 mg/dL)	9/13
Hypofibrinogenemia (< 200 mg/dL)	7/13
One of the above	10/13
Both of the above	6/13
Low/absent NK cell activity	2/4

Table 2: Patients meeting HLH-2004 Criteria.

Of note, none of the 3 subjects who failed to meet criteria had sIL-2R tested at our center, and all were missing confirmatory laboratory data. As shown in (Table 3), nine patients (60%) died, with a median time from diagnosis to death of 37 days (range 5 to 184 days). One patient whose death was not confirmed was discharged to hospice after 313 days of follow up. The median follow up for the 6 patients who have not died was 315 days.

Characteristic	Number of Patients
Treatment	
High-dose steroids	12
Etoposide	8
Rituximab	5
IVIG	5
Cyclosporine	4
No HLH-directed treatment	3
Outcome	
Death	9
Mean time to death (days)	54.9
Median time to death (days)	37
Mean length of follow up (days) for patients who did not die	336.3 (median, 315 days)

Table 3: Treatment and Outcomes.

For the six patients whose HLH was triggered by malignancy, all of the inciting malignancies were hematologic. The subtypes represented were: extranodal NK/T-cell lymphoma (two patients), diffuse large B-cell lymphoma (one patient) peripheral T-cell lymphoma not otherwise specified (one patient), and B-cell chronic lymphocytic leukemia (one patient). The final patient whose HLH was likely triggered by malignancy had a presumed T-cell lym-

phoma; that patient was a 73-year-old man who presented with pancytopenia and diffuse lymphadenopathy; lymph node biopsy revealed necrosis but no definitive diagnosis could be made before he experienced rapid clinical deterioration. Four of the six patients with malignancy-associated HLH died. All of these patients except one were over the age of 45 years; the exception was a 24-year-old man with extranodal NK/T-cell lymphoma.

Four patients had infection as the underlying cause for HLH. EBV was associated with HLH for two patients in our series. One of these was a 26-year-old woman with AIDS who presented with fever, and following diagnosis of HLH was found to have serum EBV titer of 340 copies/uL in addition to 840 copies/uL in bone marrow. She was initially treated with etoposide, dexamethasone and rituximab, but experienced rapid clinical deterioration within several weeks of receiving chemotherapy. The other EBV patient was an 18-year-old El Salvadoran immigrant with no past medical history in whom EBV was detected in blood after EBV IgG was positive. One patient, a 60-year-old man with migraines, had a positive Herpes Simplex Virus (HSV) PCR taken from an oral lesion. He was treated for disseminated HSV but unfortunately expired despite this. The final patient for whom infection was the suspected trigger had presented after a viral prodrome; this patient reportedly had EBV positivity in serum at an outside facility that was never documented at our center. Although most were younger and did not have significant medical comorbidities, all of the patients with infection-triggered HLH died.

Three patients had underlying autoimmune disease. One patient had juvenile rheumatoid arthritis, one had adult Still's disease, and one had congenital Erythropoietic Porphyria (CEP). Of note, the patient with CEP was the only member of our case series in whom HLH resolved without treatment. None of the patients with underlying autoimmune disease died during follow up.

Patients received various components of the HLH-2004 treatment protocol. Four patients received etoposide, dexamethasone, rituximab, and IVIG. Two of these also received cyclosporine. One patient received etoposide, dexamethasone, and rituximab, in addition to intrathecal methotrexate. Three patients received only etoposide and dexamethasone and one patient received IVIG and dexamethasone. Two patients received cyclosporine and high-dose steroids; one of these also was treated with IVIG. One patient received only steroids. Three patients did not receive any therapy directed at HLH. Of these, one patient experienced resolution of HLH, and the other two experienced rapid clinical deteriorations before treatment could be started. Three out of four patients who received cyclosporine died. Only one patient in our case series underwent stem cell transplant; that patient was discharged to hospice and is presumed to have died.

Discussion

HLH is a devastating clinical syndrome whose biological underpinning is poorly understood in adults. The pathogenesis involves an inappropriate immune response mediated through uncontrolled NK and T-cell activation by antigen-presenting cells [4-11], leading to hypersecretion of proinflammatory cytokines [3-8].

Timely diagnosis of HLH is difficult in clinical practice. Diagnosis has traditionally been made by having one of the known genetic defects or by meeting 5 of 8 criteria proposed by HLH-94 (and subsequently HLH-2004) clinical trials conducted in children [5]. Criteria include fever > 38.5 C, splenomegaly, cytopenias (at least 2 of 3 lineages), hypertriglyceridemia > 265 mg/dL (2.99 mmol/L) and/or hypofibrinogenemia < 150 mg/dL (4.41 umol/L), hemophagocytosis in bone marrow, spleen, lymph nodes or liver, ferritin > 500 ng/mL, low or absent NK-cell activity, and elevated sCD-25 (also known as soluble IL-2 receptor). 80% of our patients met HLH-2004 diagnostic criteria. The patients who did not meet criteria had missing laboratory data that affected the adjudication. Our case series suggests that the HLH-2004 criteria are a useful way to confirm a suspected diagnosis of HLH, particularly as they do not rely on the presence of hemophagocytosis. Representative examples of hemophagocytosis are presented in Figure 1. Less than half of our patients had evidence of hemophagocytosis in bone marrow or peripheral blood, consistent with a review of bone marrow aspirates from French tertiary care hospitals, in which almost 40% of aspirates with hemophagocytosis were from patients without HLH and 30% of patients with HLH did not have evidence of hemophagocytosis [7].

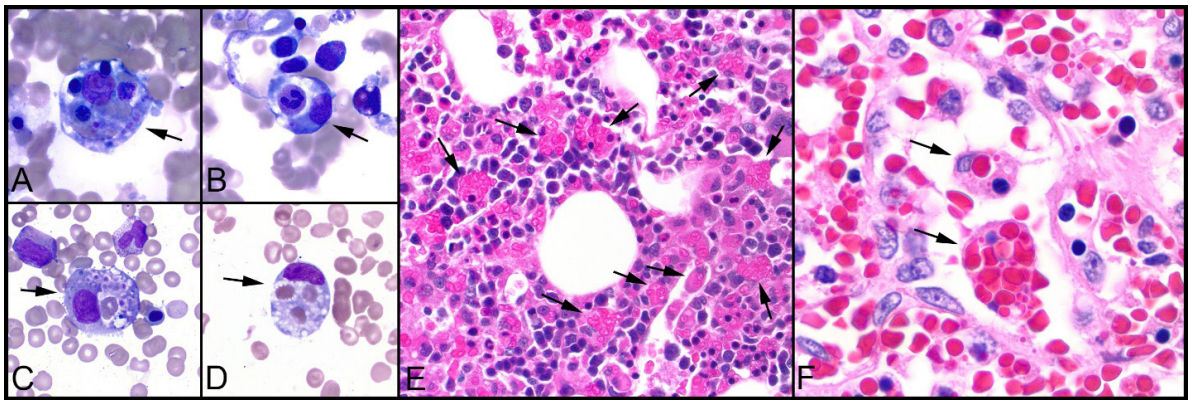

Figure 1: Hemophagocytosis. Representative images of hemophagocytosis are shown from bone marrow aspirates (A-D), bone marrow core biopsy (E), and spleen (F). Hemophagocytic histiocytes (arrows) are most often seen phagocytosing red blood cells but can also be seen with phagocytosed neutrophils (B), platelets (A, C), and lymphocytes (A, F). A, B, D: Wright-Giemsa stain, 100x oil objective; C: Wright-Giemsa stain, 50x oil objective; E: H&E, 40x objective; F: H&E, 100x oil objective.

In our case series, all patients had ferritin > 500 ng/mL and all but two had ferritin > 1900 ng/mL (4269 pmol/L). Only three patients had ferritin > 10,000 ng/mL (22,470 pmol/L). Ferritin is secreted from macrophages and involved in pro-inflammatory signaling pathways [12-13]. In one pediatric population, a ferritin cutoff of 10,000 ng/mL had a sensitivity of 90% and a specificity of 96% for the diagnosis of HLH [13], but this has not been validated in adult populations [14]. Unfortunately, ferritin is elevated in many inflammatory states, limiting its utility in diagnosing HLH.

In our case series, malignancy was the most common trigger for HLH, followed by infection and autoimmune or genetic disease. Malignancies, particularly non-Hodgkin's lymphoma, peripheral T-cell lymphomas [15], and NK-cell lymphomas, are the second-most commonly identified trigger in adults, accounting for 47% of published cases [4]. However, other malignancies such as Hodgkin disease, multiple myeloma, acute lymphoblastic leukemia, hairy cell leukemia, and carcinoma of the stomach and ovary have also been implicated [16-18]. Worldwide, infections are the most common identifiable trigger of HLH. Consistent with our case series, the best known viral association is with EBV. Cases of Hodgkin disease-associated HLH have also been linked to infection with EBV [16]. The lower proportion of patients in our series with infection as a trigger could be related to our small sample size, geographic location (lower prevalence of EBV and other infections than in Asia where many studies were performed), or the fact that our tertiary care center admits a large number of medically complex patients with hematologic malignancies.

Autoimmune diseases, including SLE, adult-onset Still's disease, mixed-connective tissue disease, rheumatoid arthritis, and Evans syndrome, are also known triggers of HLH; this entity is termed "macrophage activation syndrome" (MAS). In our series, three patients (20%) had HLH triggered by autoimmune disease; one of these had adult-onset Still's disease. Mortality for MAS in the literature ranges from 5-39% [20-22], lower than for other causes of HLH. We also found a lower mortality rate in the patients from our case series whose HLH was triggered by autoimmune disease.

The prognosis of adults with HLH is very poor, with mortality around 40-75% and median survival of approximately 2 months [4-14]. Advanced age, thrombocytopenia [4], hypoalbuminemia [9], and extended fever [23] have been previously associated with worse prognosis. Perhaps the clearest association with poor prognosis is HLH associated with malignancy (particularly lymphoma). Our case series did not deviate from these published findings; most of our patients died, and two-thirds of those with malignancy-associated HLH died.

There have been no randomized controlled trials evaluating HLH treatments in adults. The rarity of the syndrome and the challenge of a prompt diagnosis makes conduction of such studies challenging. There has been one major trial in children, HLH-94 [24], which evaluated high-dose dexamethasone (preferred over methylprednisolone due to higher central nervous system penetration), etoposide, cyclosporine A, and intrathecal methotrexate. Five-year survival improved from 4% to 54%, with survival up to 66% after hematopoietic stem cell transplant [6]. HLH-94 was then revised to HLH-2004, which added cyclosporine A to the induction phase. Treatment of HLH should start with treatment of the inciting event. Glucocorticoids are important for their ability to reduce inflammation and for their direct cytotoxic effects on T-cells. Etoposide seems to be particularly helpful in the treatment of EBV-associated HLH [25], and rituximab can be considered in this setting given the theoretical benefit of clearing viral reservoirs. Both of the patients in our series with EBV-associated HLH received etoposide and rituximab. For non-responders, hematopoietic stem cell transplant remains the only long-term treat-

ment option. Despite one patient in our series receiving a stem cell transplant, her outcome was poor.

Conclusion

Hemophagocytic lymphohistiocytosis is a devastating clinical syndrome incited by excessive immune activation and inflammation, most commonly in response to viral infection, malignancy, or autoimmune disease, manifested clinically by fevers, cytopenias, renal and liver failure, neurologic change, lymphadenopathy, and hyperferritinemia. The classical pathologic finding of hemophagocytosis is neither sensitive nor specific. In our case series, malignancy and infection were the most common inciting events, with malignancy having a very high mortality. Initial diagnostic efforts should be focused on finding the underlying etiology for HLH, as treatment relies on the mainstay of high-dose dexamethasone plus targeted agents based on the etiology (i.e. etoposide and rituximab for EBV-associated cases, appropriate chemotherapy regimens for malignancy-associated cases). Our series identifies the need for multi-center randomized clinical trials to delineate the best initial therapies.

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