

Hemophagocytic Lymphohistiocytosis in Adults: Two Instructive Cases

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening condition characterized by pathological immune activation leading to extreme inflammation and organ damage including cytopenias, hepatitis, coagulopathy, and central nervous system damage. It occurs most commonly in children, often as a familial disorder, and is very rare in adults, where it tends to be sporadic. Two exemplary cases of adult HLH are presented here, illustrating the clinical features, treatment and natural history of this aggressive and often fatal disease. A 21-year-old man presented with jaundice and fever and was found to have cytomegalovirus-triggered HLH. He responded well to the HLH-2004 protocol and remains in remission. A 55-year-old woman presented with erythroderma and multi-organ failure and was found to have HLH associated with an abnormal T cell population and low-titre Epstein-Barr virus. She died despite etoposide (Etopophos)-based therapy. HLH should be considered in patients with persistent unexplained inflammation, cytopenias, hepatitis, and coagulopathy. Serum ferritin is a useful screening test and hyperferritinemia >10,000 µg/L is thought to be specific for hemophagocytosis. Tissue biopsy (bone marrow, lymph node or liver) to confirm hemophagocytosis is desirable, but hemophagocytosis is often a late finding and is not necessary for the diagnosis of HLH. Once the diagnosis is confirmed, rapid initiation of chemo-immunotherapy is required to induce remission.

KEYWORDS: *hemophagocytosis lymphohistiocytosis, adult presentation, life-threatening, organ failure, diagnosis and treatment*

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare and frequently fatal syndrome of pathological immune activation, characterized by unregulated histiocyte proliferation and hypercytokinemia.¹ This exaggerated immune and inflammatory response can present with unexplained fever, progressing to pancytopenia, elevated liver enzymes, multi-organ failure, and death. The natural history and treatment of this disease is best described in children, where historically, the median survival for familial HLH was two months. However, in the past 20 years, prospective trials conducted by the Histiocyte Society emphasizing early initiation of etoposide-based chemotherapy and consolidative allogeneic stem cell transplants for high risk patients have dramatically improved long-term survival by 50–60%.²

HLH is divided into primary (familial) and secondary subtypes. Familial HLH is associated with autosomal recessive genetic mutations and occurs primarily in children, although adult cases have been reported.³ Secondary HLH is more common in adults and is associated with predisposing and/or triggering factors. Predisposing factors include primary or acquired immunodeficiency, malignancy (particularly lymphoproliferative disorders), and autoimmune disease. Known triggers include infections, particularly Epstein-Barr virus (EBV), and medications such as etanercept (Enbrel) and alemtuzumab (Campath) (which ironically is also used to treat HLH). Viral-associated hemophagocytic syndrome occurs most commonly with EBV, although cytomegalovirus (CMV), human herpes virus 8 (HHV8), HIV, and other viruses have been reported.^{4,5} Hemophagocytic syndrome associated with systemic disease typically occurs in patients with systemic lupus erythematosus or adult onset Still's disease and is seen less frequently in patients with rheumatoid arthritis, polyarteritis nodosa, mixed connective tissue disease,

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pulmonary sarcoidosis, systemic sclerosis, Sjogren's syndrome, polymyositis, and dermatomyositis.^{6,7} This report describes two cases of HLH in adults in order to illustrate the clinical features and the importance of prompt diagnosis and therapy.

CASE REPORT 1

A 21-year-old Filipino man presented with a 10-day history of fever, headache and scleral icterus. He was previously healthy and taking no regular medications. His family history was unremarkable. The physical exam revealed a temperature of 40.7 °C and scleral icterus but was otherwise normal. His initial bloodwork, summarized in Table 1, was most remarkable for a ferritin level of >40,000 µg/L, along with elevated cholestatic liver enzymes and lactate dehydrogenase (LDH) levels.

Bone marrow biopsy revealed florid hemophagocytosis, and his CMV serology was consistent with acute infection (Table 1). MRI of the brain and lumbar puncture with cerebrospinal fluid analysis showed no evidence of central nervous system (CNS) disease. Genetic testing at the Cincinnati Children's Hospital for mutations in the genes associated with perforin-mediated cytotoxicity, including *PRF1* (perforin), *UNC13D* (munc13-4), *STX11* (syntaxin) or *STXPB2* (munc18-2), *RAB27A* (involved in Griscelli syndrome), as well as *SH2D1A* and *BIRC4* (both involved in X-linked lymphoproliferative disorder), revealed no genetic abnormality. He was diagnosed with HLH, secondary to an acute CMV infection.

This patient was started on the etoposide (Etopophos) and dexamethasone (Apo-dexamethasone) as per the HLH-2004 treatment protocol,⁸ and cyclosporine (Neoral) was later added. He also received IV ganciclovir (Cytovene) and prophylactic fluconazole (Apo-fluconazole) and trimethoprim-sulfamethoxazole (Septra). He defervesced quickly and showed no further systemic or neurological signs following the initiation of etoposide (Etopophos). Once he finished the eight-week initial therapy of the HLH-2004 protocol, he continued with etoposide (Etopophos), dexamethasone (Apo-dexamethasone), and valganciclovir (Valcyte) as per the continuation phase until his ferritin normalized, CMV DNA was negative for one month, and a repeat bone marrow biopsy showed marked improvement with rare hemophagocytic activity. Natural killer cell and cytotoxic T-lymphocyte function, and soluble IL2R and CD107A degranulation assays were also normal. He remains in complete remission one year after diagnosis.

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This exaggerated immune and inflammatory response [that is HLH] can present with unexplained fever progressing to pancytopenia, elevated liver enzymes, multi-organ failure, and death.

Table 1. Laboratory Findings of Two Cases of HLH.

Parameter	Case 1	Case 2
White blood cells	6.7 x 10 ⁹ /L	0.8 x 10 ⁹ /L
Neutrophils	4.8 x 10 ⁹ /L	0.2 x 10 ⁹ /L
Lymphocytes	1.4 x 10 ⁹ /L	0.7 x 10 ⁹ /L
Hemoglobin	150 g/L	81 g/L
Platelets	120 x 10 ⁹ /L	23 x 10 ⁹ /L
Ferritin	> 40000 mcg/L	> 40000 mcg/L
ALT	103 U/L	54 U/L
AST	144 U/L	383 U/L
ALP	226 U/L	206 U/L
GGT	478 U/L	39 U/L
LDH	783 U/L	3546 U/L
Albumin	36 g/L	13 g/L
Triglycerides	4.04 mmol/L	3.18 mmol/L
Total Bilirubin	68 U/L	16 U/L
INR	1.2	1.5
PTT	33 s	65 s
Fibrinogen	3.2 g/L	0.8 g/L
Creatinine	124 µmol/L	288 µmol/L
Urea	3.7 mmol/L	19 mmol/L
Viral studies	CMV IgM positive, IgG negative, PCR < 1000 copies/mL	EBV < 1000 copies/mL

CASE REPORT 2

A 55-year-old Caucasian female presented with a six-month history of progressive fatigue, anorexia, and generalized erythroderma. Her past medical history was unremarkable and she was not taking any medications. She presented with a temperature of 38.5 °C, a heart rate of 120/min, and an erythematous scaling rash covering over 95% of her body surface area, with increased scaling over her scalp and retention hyperkeratosis on her eyelids. Her abdomen was soft and non-tender, with splenomegaly palpable 3 cm below the costal margin. There was no peripheral lymphadenopathy, and the rest of her physical exam was unremarkable. Her initial bloodwork consisted of an elevated ferritin and LDH level, pancytopenia, acute kidney injury, hepatitis, and hypofibrinogenemia (Table 1).

Bone marrow biopsy and aspiration revealed hemophagocytosis and marked lymphocytosis (61%, reference range <20%) with abnormal immunophenotype (CD2+/c3+/s3-/4+/l5+/7-/8-/56-), although polymerase chain reaction (PCR) did not confirm a clonal T cell population. Skin biopsy did not reveal any findings diagnostic of cutaneous HLH or T cell lymphoma. CMV DNA was undetectable, and EBV DNA was < 1000 copies/mL. She was diagnosed with HLH and T cell lymphoma with cutaneous involvement was suspected. According to the HLH-2004 treatment protocol, she was started on etoposide (Etopophos) 140 mg IV administered twice weekly (75 mg/m², 50% reduced for renal impairment) and dexamethasone (Apo-dexamethasone) 40 mg orally daily. She also began intermittent hemodialysis for

her acute kidney injury, likely secondary acute tubular necrosis and tumour lysis. Over the next few days, she had a clinical and laboratory response, with improvement in her skin and declining LDH (1240 U/L) and ferritin (18,136 ug/L) levels. However, despite ongoing broad-spectrum antibacterial and antifungal therapy, she developed refractory tachycardia and distributive shock ten days after admission. An abdominal CT revealed extensive small bowel thickening consistent with enterocolitis. She was managed with comfort care and ultimately succumbed to her disease.

CONCLUSION

HLH occurs from the uncontrolled activation of T cells and macrophages, resulting in the consumption and apoptosis of various hematologic cell lines. Most of our understanding of the diagnosis and treatment of HLH is from the pediatric literature. This is an important caveat when applying “standard” diagnostic and therapeutic principles to the adult population, where prospective studies of this rare condition are non-existent. As defined by the Histiocyte Society, the diagnosis of HLH typically requires five or more clinical criteria (Table 2).⁸

The workup for HLH includes a complete blood count and differential, renal function tests, liver enzymes and liver function tests, fasting triglycerides, international normalized ratio, partial thromboplastin time, fibrinogen, and ferritin. Elevated ferritin levels (>10,000 ug/L) are reported to be 90% sensitive and 96 % specific for HLH in children,⁹ although this has not been validated in adults. Obtaining bone marrow, spleen, liver, or lymph node specimens to examine for tissue hemophagocytosis should be strongly considered, but this is often a late feature and is not necessary for the diagnosis of HLH (Table 2). Hepatic manifestations of HLH include a moderate increase in serum transaminases, pronounced cholestasis, raised serum bilirubin, and decreased serum albumin and coagulation factors.¹⁰ Liver biopsy tends to be non-specific with the proliferation of non-neoplastic macrophages. Investigations for secondary triggers of HLH include viral investigations (particularly EBV, HIV and CMV), and investigations for malignancy as clinically indicated. Molecular studies for HLH can be done at specialized centers such as the Cincinnati Children’s Hospital and include mutations in perforin (*PRF*), Munc 13-4 (*UNC13D*), syntaxin 11 (*STX11*), and others.

Table 2. Diagnostic Guidelines for HLH (adapted from Histiocyte Society). Diagnosis can be based on molecular findings or fulfillment of diagnostic criteria.

- 1) Molecular diagnosis consistent with HLH: pathologic mutations of *PRF1*, *UNC13D*, *Munc18-2*, *Rab27a*, *STX11*, *SH2D1A*, or *BIRC4*
- 2) Diagnostic criteria for HLH fulfilled (5 out of 8 criteria below)
 - Fever
 - Splenomegaly
 - Cytopenias affecting > 1 line (Hb < 90 g/L, plts < 100 giga/L, PMNs < 1.0 giga/L)
 - Fasting triglycerides > 2.65 g/L or fibrinogen < 1.5 g/L
 - Hemophagocytosis in bone marrow, spleen, lymph nodes, or liver*
 - Low or absent NK cell activity
 - Ferritin > 500 µg/L
 - Elevated soluble CD25 (aka soluble IL-2 receptor)

SOAP Note (Case 1)

Subjective

- 21-year-old male presenting with a 10-day history of fever, headache, and scleral icterus

Objective

- Temp 40.7 °C, scleral icterus; otherwise unremarkable physical exam
- Initial bloodwork: elevated ferritin level (> 40,000 µg/L), normal CBC and differential
- Mildly elevated liver enzymes (cholestatic), creatinine, and LDH levels
- Bone marrow biopsy revealed hemophagocytosis; CMV IgM serology positive

Assessment

- Hemophagocytic lymphohistiocytosis, triggered by acute CMV infection

Plan

- Etoposide (Etopophos) and dexamethasone (Apo-dexamethasone), then cyclosporine (Neoral) (HLH-2004 Treatment Protocol)
- Ganciclovir (Cytovene) for CMV, fluconazole (Apo-fluconazole) and trimethoprim-sulfamethoxazole (Septra) for prophylaxis
- Continuation phase of therapy; patient remains in remission one year after diagnosis

SOAP Note (Case 2)

Subjective

- 55-year-old female presenting with six-month history of progressive fatigue, anorexia, and generalized erythroderma

Objective

- Temp 38.5°C with tachycardia, generalized erythematous scaling rash, and splenomegaly
- Initial bloodwork: elevated ferritin level (> 40,000 µg/L), pancytopenia
- Elevated liver enzymes (mixed), significantly elevated creatinine and LDH levels
- Bone marrow biopsy revealed hemophagocytosis with marked lymphocytosis

Assessment

- Hemophagocytic lymphohistiocytosis, with suspected T cell lymphoma

Plan

- Etoposide (Etopophos) and dexamethasone (Apo-dexamethasone) (HLH-2004 Treatment Protocol)
- Hemodialysis for acute kidney injury
- Managed with comfort care and ultimately succumbed to her disease

The HLH treatment protocols involve early administration of chemotherapy (i.e. etoposide (Etopophos)) and dexamethasone (Apo-dexamethasone), with dose adjustment for patients with renal failure.⁸ Cyclosporine (Neoral) is part of the protocol, but is often withheld until the patient’s clinical status and renal function improve.⁸ Patients with viral-associated hemophagocytic syndrome should receive appropriate anti-viral therapy such as ganciclovir (Cytovene) for CMV. Other interventions include intrathecal therapy with methotrexate (Trexall) and prednisolone (Apo-prednisone) in patients with evidence of CNS disease, as well as supportive therapy with antimicrobial prophylaxis and intravenous immunoglobulins (IVIg).^{5,8} Rituximab (Rituxan), an anti-CD20 monoclonal antibody, has been used to suppress EBV-infected B cells in HLH. Initial treatment is given for eight weeks, and patients with persistent disease or an underlying genetic

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abnormality (primary HLH) should go on to continuation therapy as a bridge to allogeneic stem cell transplantation. In patients with poor performance status and multi-organ dysfunction, palliation is reasonable.¹¹

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