

Critical Care

Hemophagocytic Lymphohistiocytosis in Adults: A Retrospective Case Series and Review

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ABSTRACT

Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening hyperinflammatory syndrome triggered by infections, malignancies, and autoimmune diseases, often mimicking severe sepsis and delaying diagnosis. We present a case series of three patients with HLH from distinct etiologies to highlight diagnostic challenges, management, and outcomes, along with a review of HLH.

Case Series

Case 1 involved pregnancy-related HLH with delayed diagnosis and death prior to HLH-directed therapy. Case 2 involved autoimmune-associated HLH in patient with previous HLH secondary to Legionella infection, treated with the HLH-94 protocol with survival. Case 3 involved lymphoma-associated HLH with parvovirus B19, resulting in death despite treatment.

Discussion

Persistent fever despite antimicrobial therapy and elevated CXCL9 levels were observed in all cases, with higher levels associated with worse outcomes. Median time to HLH consideration was 10 days.

Conclusion

HLH remains diagnostically challenging with limited tools. Early recognition and multidisciplinary management are essential to improve outcomes.

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a hyperinflammatory state caused by overactivation of multiple white blood cell lines presenting with devastating consequences including multi-organ failure and death.¹ The pathophysiology of HLH stems from dysregulation of the termination of the normal immune system response. In a normal immune response to infection, including sepsis, natural killer and CD8+ T cells kill infected cells using the perforin-granzyme pathway, which self-terminates.¹ In HLH, however, the excessive stimulation causes uncontrolled proliferation of CD8+ T cells and macrophage activation, leading to a cytokine storm and tissue destruction.¹

Mortality associated with HLH has been reported to be as high as 57.8%,² emphasizing the need for prompt and accurate diagnosis. Our case series seeks to contribute to the limited body of data on HLH by providing demographic characteristics, diagnostic workups, treatment regimens provided, and outcomes for HLH patients managed at a tertiary care center.

CASE SERIES

Patient 1

A 20-year-old non-Hispanic white primigravid woman at 34 weeks and 1 day gestation complicated by class III obesity and metabolic dysfunction-associated steatotic liver disease (MASLD) with a recent diagnosis of COVID-19 presented to the antepartum unit with decreased fetal movement and a low-grade fever. On admission, vital signs included a temperature of 37.6C, heart rate of 133 bpm, respiratory rate of 20/min, and blood pressure of 107/55 mmHg. Laboratory studies demonstrated elevated AST and ALT. Physical exam was notable only for splenomegaly. A biophysical profile scored 2/8, and a transvaginal ultrasound revealed a 1 cm cervix with fluid dilation but was otherwise unremarkable. She was admitted for monitoring.

Three days into admission, the patient delivered a premature but otherwise healthy female infant. Postpartum, she developed worsening tachycardia and fever up to 39.8°C. CT angiography ruled out pulmonary embolism, and EKG was normal. The patient went into lactic acidosis and was transferred to the intensive care unit. Broad-spectrum antibiotics were started, however AST levels contin-

ued to rise. Hepatology evaluation excluded viral, autoimmune, and vascular causes of hepatitis, along with acute fatty liver of pregnancy and hemolysis, and elevated liver enzymes and low platelets (HELLP) syndrome, given leukopenia with left shift and fever.

CT of the abdomen and pelvis, along with pelvic ultrasound, were performed, suggesting possible retained products of conception. After multidisciplinary discussion, dilation and curettage (D&C) was pursued. However, no retained products were identified.

Post-procedure, the patient continued to decline. Given the unclear etiology of her progressive decline and concern for HLH, rheumatology was consulted for further evaluation. However, before diagnostic workup could be completed, the patient deteriorated further and subsequently expired. Subsequent results after her death met diagnostic criteria for HLH.

Patient 2

A 44-year-old Hispanic woman with a history of hemophagocytic lymphohistiocytosis (HLH) secondary to *Legionella pneumophila* infection presented to the emergency department with progressive nausea, generalized weakness, and poor oral intake. Two years earlier, she had been treated at an outside hospital with the HLH-94 protocol for HLH secondary to *Legionella* pneumonia. Given her history, unstable vital signs, and high suspicion for recurrence, she was admitted directly to the intensive care unit (ICU), and hematology/oncology was consulted.

On admission, vital signs revealed a blood pressure of 88/52 mmHg, oxygen saturation of 93%, respiratory rate of 23 breaths/min, temperature of 37.7°C, and heart rate of 104 beats/min. Laboratory evaluation demonstrated significant neutrophilic leukocytosis and anemia. Empiric broad-spectrum antibiotics were initiated given concern for sepsis.

Hematology/oncology was consulted on the case due to the high suspicion of HLH. Lab results showed markedly elevated ferritin, triglycerides, and soluble IL-2 receptor levels, though bone marrow biopsy did not show hemophagocytosis. Infectious workup, including blood cultures, remained negative. 20 mg of dexamethasone daily was initiated, and the patient's leukocytosis decreased while the blood pressure slowly increased.

Rheumatology was consulted given the high suspicion for an autoimmune etiology for the HLH, given the negative infectious and malignancy workup. They ultimately determined that the patient met Yamaguchi and Fautrel criteria for adult-onset Still's disease, and recommended continued corticosteroid therapy and consideration of canakinumab on an outpatient basis. The patient's clinical status gradually improved, and she was discharged on day ten of admission with dexamethasone 20 mg daily and hematology/oncology follow-up.

Patient 3

A 47-year-old woman with no significant past medical history was transferred to the ICU for higher-level hematology/oncology evaluation of suspected hemophagocytic lymphohistiocytosis (HLH) secondary to possible T-cell lymphoma. Nine days prior, she had presented to an outside hospital with pancytopenia and leukocytosis concerning acute leukemia. Bone marrow biopsy at that time demonstrated abundant hemophagocytic histiocytes, raising suspicion for HLH in the setting of a possible underlying lymphoma. She was then transferred to our ICU for further diagnostic workup and management.

Upon transfer, her vitals demonstrated a blood pressure of 111/74 mmHg, respiratory rate of 22 breaths per minute, oxygen saturation of 100% on 2L/minute nasal cannula, temperature of 38.3 °C, and a heart rate of 130 beats per minute. Physical exam showed a diffusely and mildly distended abdomen but no other abnormalities. Labs were significant for severe pancytopenia, mild hyponatremia, and significant elevations in transaminases. Repeated bone marrow biopsy confirmed anaplastic large cell lymphoma and hemophagocytic activity, along with parvovirus B19 DNA was confirmed with PCR. Hematology/oncology recommended starting the patient on 40 mg dexamethasone daily along with three rounds of etoposide. However, the patient's encephalopathy worsened over the course of her admission, leading to her death eight days later via cerebral hemorrhage.

Objective data, including laboratory results and physician exam findings, for all patients are presented in [Table 1](#). All patients experienced a fever despite proper antimicrobial coverage, and the average time from diagnosis to treatment was 10 days.

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DISCUSSION

This case series highlights presentations of HLH due to various etiologies and compares their severity to each other, demonstrating how heterogeneous HLH may present. However, there are shared findings across cases. All patients had recurrent fevers despite appropriate antimicrobial therapy, attributable to the non-infectious pathophysiology of HLH, along with elevated soluble CD25 levels. HLH should be suspected in all patients who present with a sepsis-like illness refractory to treatment, with signs such as hepatosplenomegaly, cytopenias, persistent fevers, and markedly elevated ferritin levels.¹

Patient 1 demonstrates how the diagnosis of HLH can be obscured by multiple confounding variables, such as complications with pregnancy and a recent COVID-19 diagnosis. Initial suspicion was directed toward sepsis secondary to endometritis, delaying HLH-specific evaluation. This reflects a common challenge in HLH, where overlapping features with other inflammatory conditions often lead to delayed recognition. Specifically, pregnancy-related HLH may be challenging to diagnose due to similarities in presentation with conditions such as HELLP syndrome, acute fatty liver of pregnancy, and pre-eclampsia, often leading to missed HLH diagnoses in this population.³

Patient 2 highlights the association between adult-onset Still's disease (AOSD) and HLH. HLH in the setting of AOSD is often described as macrophage activation syndrome

Table 1. Pertinent lab values for each patient.

Parameter	Patient 1	Patient 2	Patient 3
Temperature (peak value)	42.5°C	37.9°C	38.3°C
Cytopenia? (at least 2 lineages) Hgb<90g/L, Plt <100x10 ⁹ /L, Neutrophils <109/L	Yes	No	Yes
Deficient Lineages	Hgb 8.5 g/dL, Plt 75K/uL	N/A	WBC 0.9, Plt 24, Hgb 7.8
Splenomegaly?	Yes	No	No
Hypofibrinogenemia or Hypertriglyceridemia (Fibrinogen =<1.5g/L, Triglyceride >= 3.0 mmol/L)	Yes (Fibrinogen 38mg/dL, Triglycerides 1579 mg/dL)	Yes (Fibrinogen 101 mg/dL, Triglycerides 195 mg/dL)	Yes (Fibrinogen 116, Triglycerides 346)
Hyperferritinemia =>500 microg/l	Yes, 23175 ng/mL	Yes, 7462 ng/mL	Yes, >100,000
Hemophagocytosis (bone marrow or other tissues)	Not performed	No evidence of hemophagocytosis	Anaplastic large cell lymphoma; Background trilineage hypoplasia with abundant hemophagocytic histiocytes.
Elevated Soluble CD25 (soluble IL-2) >= 2400 units/ml?	Yes	Yes	Yes
Soluble CD25 (IL2-R) level	11,735 U/mL	12275 pg/mL	>20,000 pg/mL
Elevated CXCL9?	Yes	Yes	Yes
CXCL9 level pg/mL	>608,000	9652	440,846
Reduced or absent NK cell activity?	No	No	No
Elevated LFTs? (peak value in U/L)	Yes; 6,168 AST & 689 ALT	Yes; 239 AST & 115 ALT	Yes; 899 AST & 491 ALT
Elevated LDH? (peak value in U/L)	Yes; >2500	Yes; 2445	Yes; >2500
Elevated d-dimers? (peak value in ng/mL)	Yes; >7650	Yes; 5411	Yes >7650
Known underlying immunosuppression?	No	No	No
Identified Trigger? (Infection, cancer, Rheumatologic disorder, immunodeficiencies)	COVID-19 & pregnancy	Legionella for the first episode followed by adult-onset Still's disease for the second episode	Anaplastic large cell lymphoma
Infectious etiologies?	None	None	Complicated by parvovirus B19
Autoimmune workup?	Negative workup	ANA antibodies 1:320	Negative
Presenting symptom	Intermittent fever, cough, shortness of breath, transaminitis attributed to NAFLD	Fevers, chills, nausea, diarrhea, fatigue	Nausea, vomiting, diarrhea
H score	259	178	202
OHI Index	Meets criteria	Meets criteria	Meets criteria
Time from presentation to diagnosis of HLH?	20 days	5 days	10 days
Treatment regimen	Dexamethasone 10 mg twice daily	Dexamethasone 20 mg daily	Dexamethasone 40 mg once daily, three sessions of etoposide
Outcome	Death	Survived	Death

(MAS), a subtype of HLH that has been reported to present with relatively higher fibrinogen levels compared to other HLH variants.⁴ Interestingly, this patient's fibrinogen level was similar to that in our other cases, suggesting that MAS may not always follow the expected laboratory profile. Additionally, recurrent HLH has been associated with increased mortality. However, this patient experienced a less

severe disease course and survived, likely due to early recognition of HLH and early initiation of therapy.

Patient 3 demonstrates the severity of HLH when associated with lymphoma. Lymphomas are the most common malignancies associated with HLH⁵; when this occurs, the syndrome is termed lymphoma-associated hemophagocytic syndrome (LAHS). LAHS carries a worse prognosis com-

Table 2. Parameters for the revised HLH-2004 criteria, HScore (with specific scoring parameters being shown in [Table 3](#)), and the Optimized HLH Inflammatory (OHI) index.

Tool	Parameters	Interpretation
Revised HLH-2004 Criteria ⁸	Fever, splenomegaly, cytopenias (low levels of ≥ 2 cell lines), ferritin ≥ 500 ng/mL, triglycerides/fibrinogen, NK activity, soluble CD25 ≥ 2400 U/mL, hemophagocytosis seen on bone marrow biopsy	HLH diagnosis is supported by meeting ≥ 5 of 8 criteria
Hscore ⁹	See Table 3	A score ≥ 169 indicates $>93\%$ possibility of HLH
OHI Index ¹⁰	Soluble CD25 (soluble IL-2R) $>3,900$ U/m AND Ferritin $>1,000$ ng/mL	High likelihood of HLH being leading diagnosis

pared to HLH of other etiologies, with reported mortality of 50.4% versus 36.4% and five-year survival of 21.5% versus 52.4%.⁶ This poor prognosis is thought to reflect the underlying pathophysiology, as repeated antigenic stimulation from lymphoma cells creates an exaggerated T-cell-mediated inflammatory response.⁷ In our series, Patient 3 mounted a robust inflammatory response with hyperferritinemia, elevated soluble CD25, and elevated CXCL9 levels, yet his HScore was lower than that of Patient 1, reflecting how malignancy-driven HLH can have devastating outcomes even when clinical scoring systems do not predict the highest severity.

Scoring tools used to support the diagnosis of HLH include the revised HLH-2004 criteria, the HScore, and the Optimized HLH Inflammatory (OHI) index (Tables 2 and 3).⁸⁻¹⁰ In a study of 13 published cohorts, Lachmann et al. demonstrated that meeting four of eight revised HLH-2004 criteria yields a sensitivity of 83.8% and specificity of 87.8%, while an HScore ≥ 169 confers 82.4% sensitivity and 87.6% specificity for HLH.¹¹ Despite their strong diagnostic performance, these tools have limitations, particularly in patients with underlying hematologic malignancies. Two of the parameters used, ferritin and soluble CD25, can be elevated in both hematologic malignancy-related inflammation and HLH.

To elaborate further, the ferritin and soluble CD25 cutoffs in the revised HLH-2004 criteria are not high enough to differentiate elevations in these markers attributable to inflammation in hematologic malignancy without HLH from true HLH. The HScore, while incorporating ferritin, does not include soluble CD25.⁹ The OHI index, developed in 2021, attempts to address these limitations by incorporating higher cutoff values for ferritin and soluble CD25, allowing for more specificity in cases of suspected HLH in hematologic malignancy.¹⁰ However, all these tools are typically applied only after HLH is clinically suspected. Because the initial presentation of HLH is often vague and nonspecific, reliance on these scoring systems may contribute to delays in diagnosis and treatment, leading to worsening mortality in patients.¹²

CXCL9, also known as monokine induced by interferon gamma (MIG), is a cytokine that plays a role in inflammation and can be used as a surrogate marker of interferon- γ .¹³ Levels of CXCL9 correlated with the severity of disease when comparing each patient in our study. Patients 1 and 3 had severe clinical outcomes and eventual death when compared to Patient 2, who, although he had a repeated

episode of HLH, survived. Literature supports the claim that CXCL9 levels correlate with disease severity, as demonstrated by Maruoka et al.¹⁴ Other laboratory values that may correlate with HLH severity include soluble interleukin-2 (CD25) and ferritin.^{15,16} While levels of these three inflammatory mediators correlate with disease severity, data on which lab value is superior to the others are lacking.

Bone marrow biopsy remains an important component in the evaluation of HLH. However, it is not sufficient to exclude HLH on its own. The presence of hemophagocytosis on biopsy has been reported to have a sensitivity of up to 83% but a specificity of only 60%, as this finding may also occur in other inflammatory or reactive states.¹⁷ Furthermore, hemophagocytosis may be absent in the early stages of HLH, limiting its utility in initial diagnosis.¹⁷ While bone marrow biopsy alone is not enough to diagnose HLH, it remains a critical data component for ruling out HLH and determining HLH severity.

Treatment for HLH has not been well deciphered in the literature. Initial HLH therapy typically consists of glucocorticoids with or without IVIG.¹⁸ The HLH-94 protocol, developed by the Histiocyte Society, suggests etoposide at 150 mg/m² twice weekly for two weeks followed by weekly, dexamethasone 10 mg/m²/day tapered over 8 weeks, and cyclosporine A introduced at 9 weeks, titrated to achieve therapeutic levels.⁶ North American Consortium for Histology recommends initiating treatment when there is a high degree of clinical suspicion, even if scoring tools are not yet diagnostic for HLH.¹² Treating the underlying trigger is necessary to reduce the burden of HLH. A retrospective chart review published in Rheumatology demonstrated drastic improvements in outcomes for HLH patients.¹² However, there have been no randomized control trials published for the treatment of HLH to date, likely due to disease heterogeneity, diagnostic uncertainty, and ethical constraints given significant improvement with the HLH-94 protocol studied in uncontrolled environments.

CONCLUSION

HLH is a severe hyperinflammatory syndrome with high mortality. Its nonspecific presentation can delay both recognition and treatment. Further research is needed to improve early diagnosis and reduce associated mortality.

Table 3. HScore scoring components. Total score range: 0–337. An HScore ≥ 169 has a sensitivity of 82.4% and specificity of 87.6% for the diagnosis of reactive hemophagocytic syndrome.

Parameter	Category	Points
Known underlying immunosuppression (e.g., HIV, long-term immunosuppressive therapy)	No	0
	Yes	18
Temperature	38.4°C (101.1°F)	0
	38.4–39.4°C (101.1–102.9°F)	33
	>39.4°C (>102.9°F)	49
Organomegaly	No	0
	Hepatomegaly or splenomegaly	23
	Hepatomegaly and splenomegaly	38
Number of cytopenias (Hb ≤ 9.2 g/dL, WBC $\leq 5,000/\text{mm}^3$, platelets $\leq 110,000/\text{mm}^3$)	1 lineage	0
	2 lineages	24
	3 lineages	34
Ferritin (ng/mL)	2,000	0
	2,000–6,000	35
	>6,000	50
Triglycerides (mmol/L)	1.5 (132.7 mg/dL)	0
	1.5–4.0 (132.7–354 mg/dL)	44
	>4.0 (>354 mg/dL)	64
Fibrinogen (g/L)	>2.5 (>250 mg/dL)	0
	≤ 2.5 (≤ 250 mg/dL)	30
AST (U/L)	30	0
	≥ 30	19
Hemophagocytosis on bone marrow aspirate	No	lan
	Yes	35

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REFERENCES

- Konkol S, Killeen RB, Rai M. Hemophagocytic lymphohistiocytosis. In: *StatPearls*. StatPearls Publishing; 2025. Accessed June 2025. <https://www.ncbi.nlm.nih.gov/books/NBK557776/>
- Knaak C, Nyvlt P, Schuster FS, et al. Treatment and mortality of hemophagocytic lymphohistiocytosis in critically ill adult patients: a systematic review with pooled analysis. *Crit Care Med*. 2020;48(11):e1137-e1146. doi:[10.1097/CCM.0000000000004581](https://doi.org/10.1097/CCM.0000000000004581)
- Abdelhay A, Eltaher B, Reghis M, et al. Hemophagocytic lymphohistiocytosis in pregnancy: a systematic review of case reports and case series. *Am J Hematol*. 2025;100(10):1828-1838. doi:[10.1002/ajh.70013](https://doi.org/10.1002/ajh.70013)
- Ruscitti P, Rago C, Breda L, et al. Macrophage activation syndrome in Still's disease: analysis of clinical characteristics and survival in paediatric and adult patients. *Clin Rheumatol*. 2017;36(12):2839-2845. doi:[10.1007/s10067-017-3830-3](https://doi.org/10.1007/s10067-017-3830-3)
- Jordan MB, Allen CE, Greenberg J, et al. Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: recommendations from the North American Consortium for Histiocytosis (NACHO). *Pediatr Blood Cancer*. 2019;66(11):e27929. doi:[10.1002/pbc.27929](https://doi.org/10.1002/pbc.27929)
- Zhang Q, Wang L, Zhou D, et al. Clinical features and prognostic analysis of lymphoma-associated hemophagocytic syndrome: a report of 139 caseres. *Oncol Lett*. 2022;25(1):13. doi:[10.3892/ol.2022.13599](https://doi.org/10.3892/ol.2022.13599)
- Setiadi A, Zoref-Lorenz A, Lee CY, Jordan MB, Chen LYC. Malignancy-associated haemophagocytic lymphohistiocytosis. *Lancet Haematol*. 2022;9(3):e217-e227. doi:[10.1016/S2352-3026\(21\)00366-5](https://doi.org/10.1016/S2352-3026(21)00366-5)
- Henter JI, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. 2007;48(2):124-131. doi:[10.1002/pbc.21039](https://doi.org/10.1002/pbc.21039)
- Fardet L, Galicier L, Lambotte O, et al. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. *Arthritis Rheumatol*. 2014;66(9):2613-2620. doi:[10.1002/art.38690](https://doi.org/10.1002/art.38690)
- Zoref-Lorenz A, Murakami J, Hofstetter L, et al. An improved index for diagnosis and mortality prediction in malignancy-associated hemophagocytic lymphohistiocytosis. *Blood*. 2022;139(7):1098-1110. doi:[10.1182/blood.2021012764](https://doi.org/10.1182/blood.2021012764)
- Lachmann G, Heeren P, Schuster FS, et al. Multicenter validation of secondary hemophagocytic lymphohistiocytosis diagnostic criteria. *J Intern Med*. 2025;297(3):312-327. doi:[10.1111/joim.20065](https://doi.org/10.1111/joim.20065)
- Posas-Mendoza TF, McLeod C, Davis W, et al. Etiologies and management of haemophagocytic lymphohistiocytosis: is it time for an updated protocol and targeted treatments? *Rheumatology (Oxford)*. 2021;60(6):2927-2933. doi:[10.1093/rheumatology/keaa804](https://doi.org/10.1093/rheumatology/keaa804)
- Neo SY, Lundqvist A. The Multifaceted Roles of CXCL9 Within the Tumor Microenvironment. *Adv Exp Med Biol*. 2020;1231:45-51. doi:[10.1007/978-3-030-36667-4_5](https://doi.org/10.1007/978-3-030-36667-4_5)
- Maruoka H, Inoue D, Takiuchi Y, et al. IP-10/CXCL10 and MIG/CXCL9 as novel markers for the diagnosis of lymphoma-associated hemophagocytic syndrome. *Ann Hematol*. 2014;93(3):393-401. doi:[10.1007/s00277-013-1878-y](https://doi.org/10.1007/s00277-013-1878-y)
- Wimmer T, Mattes R, Stemmler HJ, et al. sCD25 as an independent adverse prognostic factor in adult patients with HLH: results of a multicenter retrospective study. *Blood Adv*. 2023;7(5):832-844. doi:[10.1182/bloodadvances.2022007953](https://doi.org/10.1182/bloodadvances.2022007953)
- Henter JI. Hemophagocytic lymphohistiocytosis. *N Engl J Med*. 2025;392(6):584-598. doi:[10.1056/NEJMr2314005](https://doi.org/10.1056/NEJMr2314005)
- Ramos-Casals M, Brito-Zerón P, López-Guillermo A, Khamashta MA, Bosch X. Adult haemophagocytic syndrome. *Lancet (London, England)*. 2014;383(9927):1503-1516. doi:[10.1016/S0140-6736\(13\)61048-X](https://doi.org/10.1016/S0140-6736(13)61048-X)
- Henter JI, Aricó M, Egeler RM, et al. HLH-94: a treatment protocol for hemophagocytic lymphohistiocytosis. *Med Pediatr Oncol*. 1997;28(5):342-347.