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Clinical Hemophagocytic Lymphohistiocytosis (HLH): A Case Series

[1]Dr. Rishika R Reddy; [2]Dr. Naveen Angadi ; [3]Dr. Rohan Bhise

[1]Authors:*
[2]Guide: MD General Medicine,
[3]Co-Guide: MBBS, MD (General Medicine), DM (Oncology)

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Abstract: Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening hyperinflammatory syndrome characterized by excessive immune activation. Despite being historically associated with pediatric populations, HLH is increasingly recognized in adults, albeit with diagnostic and therapeutic challenges. This case series evaluates seven adult patients diagnosed with HLH, exploring their clinical presentation, diagnostic challenges, and treatment outcomes. Our findings highlight the need for improved awareness, timely diagnosis, and a tailored approach to managing adult HLH.

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I. INTRODUCTION

HLH is a heterogeneous group of disorders marked by an overactive immune system involving CD8+ T cells and macrophages, leading to an excessive but ineffective inflammatory response. The failure of the negative feedback loop results in persistent immune activation. First described in 1939 by Scott and Robb Smith, HLH is now recognized across all age groups. An observational study in Japan identified that 40% of HLH cases occur in adults. The estimated yearly incidence is approximately 1 per 800,000 in Italy, Sweden, and the USA, with a male-to-female ratio of 1:7 and a mean age at diagnosis of 50 years.

➢ *Pathophysiology*

The underlying mechanism of HLH, both genetic and reactive, is a defect in granule-mediated cytotoxicity, crucial for cell apoptosis. The perforin and Fas systems regulate dendritic cell homeostasis and restrict T cell activation via antigen presentation. Enhanced antigen presentation, coupled with repeated interferon-gamma-dependent stimulation of Toll-like receptors, triggers uncontrolled activation of antigen-presenting cells and T cells. This leads to hypersecretion of pro-inflammatory cytokines such as interferon-gamma, TNF-alpha, and interleukins (IL-1, IL-4, IL-6, IL-8, IL-10, IL-18), resulting in a cytokine storm.

➢ *Classification of HLH*

The differentiation between true HLH and HLH-mimics remains a diagnostic challenge. Not all patients with HLH-like clinical features have underlying immune dysregulation or benefit from immunosuppressive therapy.

Hence, HLH cases should be classified into:

- HLH DISEASE- Cases exhibiting distinct immune dysregulation and responding to immunosuppressive treatment.
- HLH MIMICS- Conditions resembling HLH but lacking clear evidence of immune dysregulation, often requiring alternative therapeutic approaches.

II. MATERIALS AND METHODS

This is a descriptive, observational study conducted between May 2023 and March 2024. Seven adult patients who met the modified HLH criteria were included. Diagnostic criteria were based on clinical suspicion and serum ferritin levels.

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Molecular diagnosis of hemophagocytic lymphohistiocytosis (HLH) or X-linked lymphoproliferative syndrome (XLP).	
Or at least 3 of 4:	Fever
	Splenomegaly
	Cytopenia (minimum 2 cell lines reduced)
	Hepatitis
And at least 1 of 4:	Hemophagocytosis
	Increased Ferritin
	Increased sIL2Rα (age based)
	Absent or very decreased NK function
Other results supportive of HLH diagnosis:	Hypertriglyceridemia
	Hypofibrinogenemia
	Hyponatremia

HLH diagnostic criteria, 2009.

III. RESULTS

All seven patients presented with clinical suspicion of HLH. Serum ferritin levels were obtained for confirmation. Additional laboratory and imaging studies were performed to rule out differential diagnoses and identify potential underlying triggers.

CLINICAL FEATURES	%OF PATIENTS
FEVER	100
CYTOPENIA	100
SPLENOMEGALY	57 (4/7)
THROMBPCYTOPENIA	100
HEPATITIS	71.4 (5/7)
HYPERFERRITINEMIA	100
HEMOPHAGOCYTOSIS	28.5(2/7)
HYPONATREMIA	71.4(5/7)
ON DIALYSIS	28.5 (2/7)

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ACCORDING TO MODIFIED 2009 HLH CRITERIA							
CASE	**1**	**2**	**3**	**4**	**5**	**6**	**7**
AT LEAST THREE OF THE FOLLOWING							
FEVER	+	+	+	+	+	+	+
SPLENOMEGALY	_	_	+	+	+	-	+
CYTOPENIA	+	+	+	+	+	+	+
HEMOGLOBIN	8.2	14.1	11	8.8		7.1	11.4
PLATELET	99000	14000	30000	33000		13000	43000
TOTAL LEUCOCYTE COUNT	1700	5800	1800	1500		2700	1200
HEPATITS	+	+	+				+
SGOT	387	5844	234	112		122	262
SGPT	183	1360	179	60		35	139
ALKALINE PHOSPHATASE	362	76					
AT LEAST ONE OF THE FOLLOWING							
FERRITIN	40970	39144	100000	45432	100000	34088	16326
ELEVATED SOLUBLE CD25/SOLUBLE IL2 RECEPTOR	NA	NA	NA	NA	NA	NA	NA
HEMOPHAGOCYTOSIS ON TISSUE BIOPSY	NA	NA	NA	NA	+	NA	NA
LOW OR ABSENT NK CELL ACTIVITY	NA	NA	NA	NA	NA	NA	NA
OTHER SUPPORTIVE FEATURES							
HYPERTRIGLYCERIDEMIA	283	387	NA	NA			
HYPOFIBRINOGENEMIA	NA	168	NA	NA			
HYPONATREMIA	120	145	126	133		128	124

EPIDEMIOLOGICAL FEATURES	
MEAN AGE	37.7 YEARS
MALE	71.4%
FEMALE	28.5%

HOSPITAL STAY – MEAN DURATION	12.8 DAYS
WARD	20% OF PATIENTS
INTENSIVE CARE	80% OF PATIENTS
NEED OF DIALYSIS	28.5% (2/7)
MORTALITY	71.48%

ONE PATIENT HAD HEMOPGAGOCYTOSIS ON BONE MARROW TRUCUT BIOPSY

ONE PATIENT HAD HEMOPHAGOCYTOSIS ON BONE MARROW ASPIRATION

➢ *Differential Diagnosis*

HLH presents a diagnostic challenge due to its overlap with severe infections, autoimmune diseases, and malignancies. Key differential considerations include:

- Severe infections(e.g., viral, bacterial, fungal, or parasitic infections)
- Autoimmune diseases (e.g., adult-onset Still's disease, systemic lupus erythematosus)
- Malignancies(e.g., histiocytic malignancies, lymphoma-associated HLH)
- Systemic inflammatory response syndrome (SIRS) and multiorgan dysfunction syndrome (MODS), which share overlapping features with HLH

IV. DISCUSSION

While HLH was initially considered a pediatric disease, emerging data suggest that adult HLH remains underdiagnosed. Milder genetic variants may manifest in adulthood following a triggering event. HLH is often

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regarded as “the masquerader” due to its diverse clinical presentation and ambiguous pathophysiology. The absence of well-defined adult-specific diagnostic criteria complicates recognition and treatment.

Some researchers propose that HLH, sepsis, SIRS, and MODS exist on a continuum of systemic immune dysregulation. The delayed diagnosis and high mortality associated with adult HLH highlight the need for increased awareness and clear clinical guidelines.

V. FUTURE PERSPECTIVES

Key considerations for advancing HLH diagnosis and treatment include:

- **Genetic Susceptibility**:Age-related variations in genetic mutations suggest that early-onset HLH is linked to truncating mutations, whereas late-onset HLH is associated with hypomorphic mutations (missense or splice-site mutations).
- **Triggering Events**: Many adults with hypomorphic mutations develop HLH only in response to additional triggers.
- **Diagnostic Challenges**: The lack of standardized adult-specific criteria results in frequent misdiagnoses.
- **Ferritin as a Screening Tool**: Ferritin levels >10,000 ng/dL are relatively specific for HLH but lack sensitivity.
- **Need for a Simple Algorithm:** A standardized diagnostic approach is essential, but its limitations must be recognized to prevent misdiagnosis and inappropriate treatment.

VI. CONCLUSION

HLH is increasingly recognized in adults but remains underdiagnosed due to ambiguous diagnostic criteria and clinical overlap with other inflammatory conditions. Prompt recognition and treatment are critical, yet caution is needed to distinguish HLH from its mimics. Greater awareness, research, and standardized guidelines are necessary to improve outcomes in adult HLH cases.

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