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Prolonged fever with cytopenias: Unmasking hemophagocytic lymphohistiocytosis

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Abstract
The hemophagocytic lymphohistiocytosis (HLH) is a syndrome with apoptosis deficiency that results in the impairment of a regulatory pathway with consequent immune and inflammatory responses. Fever, cytopenias, splenomegaly, and hemophagocytosis are cardinal signs. It may be familial or secondary to infection, autoimmunity, or neoplasia. Impaired natural killer (NK)-cell cytotoxicity is the hallmark of HLH. All genetic defects in familial HLH are related to granule-dependent cytotoxicity.
The authors present a 35-year-old male veterinary technician with no prior comorbidities who presented with a history of continuous high-grade fever for 20 days associated with chills, rigors, and generalized weakness. There were no associated respiratory, gastrointestinal, or neurological symptoms. On examination, he was hemodynamically stable with icterus and perioral crusted rashes, and abdominal examination revealed hepatomegaly and splenomegaly.
Initial laboratory evaluation demonstrated cytopenias (leukopenia and thrombocytopenia), markedly elevated inflammatory markers, deranged liver function tests, and extreme hyperferritinemia (250,000 ng/mL) with hypertriglyceridemia (705 mg/dL). Ultrasonography of the abdomen confirmed hepatosplenomegaly.
Based on clinical features and laboratory parameters fulfilling diagnostic criteria, the patient was diagnosed with secondary hemophagocytic lymphohistiocytosis (macrophage activation syndrome).
HLH is a rare and life-threatening syndrome. The delay in its diagnosis due to the variability of the clinical and laboratory findings constitutes the main obstacle to a successful prognosis, as illustrated in this case report.

Keywords: HLH, bicytopenia, hyperferritinemia

Introduction

Hemophagocytic lymphohistiocytosis (HLH), is a severe, self-sustaining inflammatory syndrome caused by an excessive, prolonged, and ineffective immune response. HLH affects children more often than adults, namely infants with less than one year of life, due to a diversity of X-linked and autosomal recessive disorders. According to the etiology, HLH can be classified into genetic/primary and acquired/secondary types. Among primary HLH types, there is a further subdivision between familial HLH and other genetically associated forms of HLH. Secondary HLH can typically be triggered by infections, malignancies (mainly haematological, such as T-cell and natural killer-cell [NK] lymphomas), autoimmune diseases, and/or immune deficiency status.
The pathophysiology of HLH remains incompletely understood. However, cytotoxic stimulation of NK cells and/or T lymphocytes results in augmented serum cytokine levels and consequent multiplication of T cells and macrophages within target organs such as bone marrow, spleen, liver, and lymph nodes.
A definite consensus on the diagnostic criteria of HLH is still lacking. The clinical characteristics of HLH are extremely heterogeneous, yet the disease commonly presents with unremitting fever, splenomegaly, and peripheral blood cytopenias.
Adults with secondary HLH have extremely elevated mortality rates and a poor prognosis. Prompt recognition, diagnosis, and treatment of HLH are key to reversing a bad prognosis.

Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially life-threatening condition characterised by Excessive activation of cytotoxic T cells and histiocytes. This immune over activation triggers an uncontrolled release of inflammatory cytokines, leading to extensive tissue injury and multiorgan dysfunction. The secondary form of HLH usually develops in response to underlying triggers such as infections, autoimmune diseases or malignancies.

Case Presentation: We present a case of a 35-year-old male patient working in a veterinary medicine department, no known co-morbidities. He presented with high-grade fever for 20 days, associated with icterus and hepatosplenomegaly. Laboratory evaluation revealed bicytopenia (TLC 1,520/µL, platelets 72,000/µL) along with elevated liver enzymes, prompting further assessment of ferritin and triglyceride levels, which demonstrated marked hyperferritinemia (250,000 ng/mL) and hypertriglyceridemia (705 mg/dL). An extensive infectious workup, including dengue, malaria, brucellosis, and leptospirosis, was negative. EBV DNA PCR showed a high viral load (4.48×10^5 copies/mL). Bone-marrow aspiration demonstrated hypocellularity with foamy histiocytes and hemophagocytes, confirming hemophagocytic lymphohistiocytosis (fulfilling HLH-2024 criteria). The patient failed to respond to broad-spectrum antibiotics (ceftriaxone, doxycycline), but showed transient improvement with corticosteroids; fever recurred upon tapering steroids. Etoposide was initiated with partial response but worsening cytopenias, necessitating rituximab and cyclophosphamide, which led to gradual clinical and hematologic improvement.

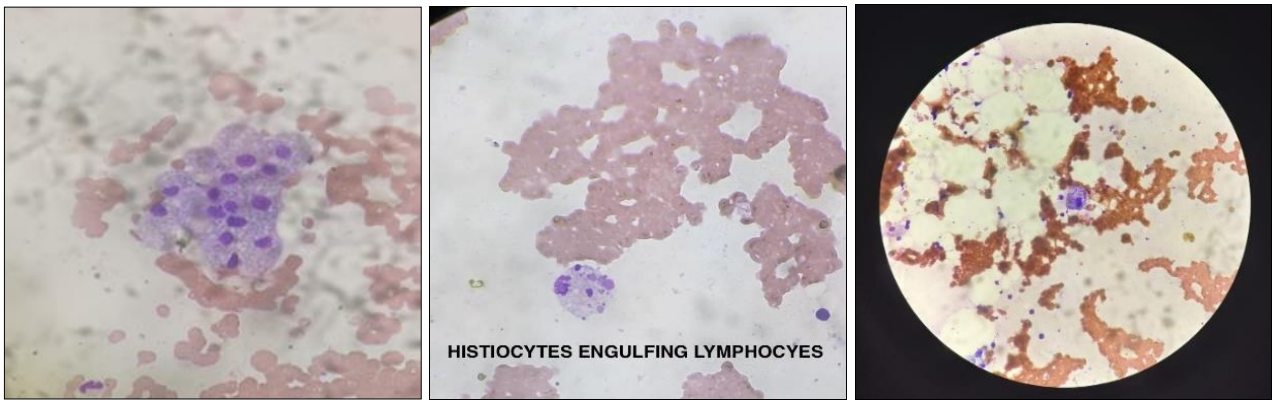

Fig 1: Bone marrow examination

Cellularity: Hypo cellular for age.
Cell trails: Poor, Diluted with peripheral blood

a. Numerous foamy histiocytes
b. Histocytes engulfing lymphocytes
c. Macrophages in marrow

Investigations

Parameter	Result	Interpretation
Hemoglobin	13.4 g/dL	Normal
Total Leukocyte Count	1520 /µL	Leukopenia
Piatelet Count	72,000 /µL	Thrombocytopenia
ESR	62 mm/hr	Elevated
Total / Direct Bilirubin	6.1 / 4.5 mg/dL	Inflammatory response
SGOT / SGPT	767 / 291 UL	Conjugated hyperbilirubinemia
ALP	1293 U/L	Elevated
Serum Ferritin	2,50,000 ng/mL	Markedly elevated
Serum Triglycerides	705 mg/dL	Hypertriglyceridemia
EBV DNA PCR (15/10/2025)	4.48×10^5 copies/mL	High viral load confirming EBV infection
USG Abdomen	Hepatomegaly,	Hepatomegaly, splenomegaly, GB wall edema

Diagnostic criteria
The diagnosis of hemophagocytic lymphohistiocytosis can be established if one of either 1 or 2 below is fulfilled:
1. A molecular diagnosis consistent with hemophagocytic lymphohistiocytosis
2. Diagnostic criteria for hemophagocytic lymphohistiocytosis fulfilled (5 out of the 8 criteria below)
Fever
Splenomegaly
Cytopenias (affecting ≥2 of 3 lineages in the peripheral blood)
Hemoglobin <9 g/dL
Neutrophils <1 × 10^9/L
Platelets <100 × 10^9/L
Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglycerides ≥3 mmol/L or ≥265 mg/dL
Fibrinogen ≤1.5 g/L
Hemophagocytosis in bone marrow, spleen, or lymph nodes
Absent or very decreased natural killer function
Ferritin ≥500 µg/L
Soluble interleukin-2 receptor ≥24,000 U/L

TABLE 1: Diagnostic criteria for hemophagocytic lymphohistiocytosis.

Conclusion

This case underscores the aggressive nature of EBV–associated HLH and emphasises the need for early recognition in patients with prolonged fever, cytopenias, and liver dysfunction unresponsive to antimicrobial therapy. HLH is a rare and life-threatening syndrome. The delay in its diagnosis, due to the variability of the clinical presentation and the insufficient specificity of the clinical and laboratory findings, constitutes the main obstacle to a successful prognosis. The broad pathogenic landscape of HLH, along with its high mortality rate, makes this disease one of the most complex disorders to manage. The development of evidence-based guidelines and novel therapies is challenging yet necessary for better outcomes in HLH. Timely escalation of immunosuppressive treatment with corticosteroids, rituximab, and cyclophosphamide can be lifesaving in refractory cases.

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