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Case Report

Hemophagocytic lymphohistiocytosis: a clinical overview and case study

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare, potentially life-threatening hyperinflammatory syndrome resulting from excessive immune activation. It is broadly classified into primary (genetic) and secondary (acquired) forms, with secondary HLH often triggered by infections, malignancies, or autoimmune diseases. The condition presents significant diagnostic challenges due to overlapping features with other systemic inflammatory disorders and sepsis. This report describes a pediatric case of HLH associated with a bacterial infection, highlighting the importance of timely diagnosis and treatment to improve outcomes. A 9-year-old female presented with persistent fever, abdominal pain, distension, facial edema, hepatosplenomegaly, and pancytopenia. Laboratory investigations revealed hyperferritinemia (18,500 ng/ml), hypertriglyceridemia (450 mg/dl), and hypofibrinogenemia (1.2 g/l). Bone marrow aspirate demonstrated hemophagocytosis. Blood cultures identified *Klebsiella pneumoniae* as the infectious trigger. The patient met six of the eight HLH-2009 diagnostic criteria, confirming the diagnosis of secondary HLH. Treatment included intravenous dexamethasone and immunoglobulin (IVIG), along with supportive care. The patient responded well, with clinical improvement and normalization of laboratory parameters. Genetic evaluation was done to exclude primary HLH and it turned out to be PRF1 gene. This case underscores the critical need for early recognition of HLH in patients presenting with fever, cytopenias, and elevated inflammatory markers. Adherence to established diagnostic criteria and prompt initiation of treatment are essential to improving survival in this severe condition. The case also highlights the role of multidisciplinary care and genetic testing in ensuring optimal long-term management.

Keywords: HLH, Hyperinflammatory syndrome, Cytopenias, Hyperferritinemia

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a severe hyperinflammatory syndrome characterized by the dysregulation of immune system activation, leading to uncontrolled cytokine release and subsequent multi-organ dysfunction. This condition can be broadly classified into two forms: primary (genetic) and secondary (acquired). Primary HLH typically results from genetic mutations affecting immune regulation pathways, such as defects in the PRF1 and UNC13D genes, which impair the cytotoxic activity of natural killer (NK) cells and cytotoxic T lymphocytes.[1,2] Secondary HLH, on the other hand, arises as a complication of infections (e.g., Epstein-Barr virus or bacterial infections), malignancies, autoimmune conditions, or immunosuppression following organ transplantation.[3]

The clinical manifestations of HLH are non-specific and can overlap significantly with other conditions, such as

severe sepsis, systemic inflammatory response syndrome (SIRS), and malignancy-associated hemophagocytic syndromes. Common presenting features include persistent fever, hepatosplenomegaly, pancytopenia, hyperferritinemia, and hypofibrinogenemia.[4] The underlying pathophysiology involves excessive activation of macrophages and lymphocytes, leading to hemophagocytosis—a hallmark diagnostic feature observed in bone marrow, liver, or lymph node biopsies.[5]

The diagnosis of HLH relies on fulfilling at least five of eight criteria outlined in the HLH-2009 diagnostic guidelines, including clinical, laboratory, and histopathological findings. These criteria are supplemented by the H score, a probability tool designed to assist in the diagnosis of HLH, particularly in adult patients.[6]

Prompt recognition and initiation of therapy are critical to improving survival, as untreated HLH carries a high mortality risk. Current therapeutic strategies include immunosuppressive agents such as dexamethasone, cyclosporine, and etoposide, as well as supportive care and targeted treatment of the underlying trigger.[7]

This report presents a pediatric case of secondary HLH triggered by *Klebsiella pneumoniae* infection, emphasizing the clinical presentation, diagnostic criteria, and management strategies employed to achieve a favorable outcome.

CASE REPORT

A 9-year-old female presented with a seven-day history of persistent high-grade fever, abdominal pain, abdominal distension, and facial edema. The patient was born to parents with a third-degree consanguineous relationship. On clinical examination, she exhibited pallor, icterus, hepatosplenomegaly, and ascites. There were no rashes, neurological deficits, or lymphadenopathy. The initial clinical suspicion was that of complicated sepsis due to her constellation of systemic inflammatory features.

Initial investigations

The patient underwent an extensive evaluation to identify the underlying cause of her symptoms. Laboratory investigations revealed as follows: complete blood count (CBC): pancytopenia, with hemoglobin at 7.5 g/dl, white blood cell count of 2,400/µl, and platelets at 80,000/µl (Table 1).

Biochemical markers

Hyperferritinemia with ferritin levels elevated to 18,500 ng/ml, hypertriglyceridemia (450 mg/dl), hypofibrinogenemia (1.2 g/l); and liver function tests (LFTs): elevated bilirubin and transaminases, suggesting hepatic involvement.

Bone marrow examination

Bone marrow aspiration, performed on 27 June 2024, from the posterior superior iliac spine, revealed hemophagocytosis within a normocellular marrow (Figures 1 and 2).

The findings confirmed the excessive phagocytosis of erythrocytes, leukocytes, and platelets, a hallmark of HLH.

Infectious workup

Blood culture identified *Klebsiella pneumoniae*, implicating it as the underlying infectious trigger. Serologic and PCR-based testing for other infectious agents, including Epstein-Barr virus (EBV), cytomegalovirus (CMV), dengue, malaria, leptospira, Rickettsial, and enteric fever, returned negative.

Diagnostic criteria fulfillment

The patient met six of the eight criteria from the HLH-2009 diagnostic guidelines, confirming the diagnosis: persistent fever >38.5°C, hepatosplenomegaly, cytopenias affecting ≥2 lineages (anemia, leukopenia, thrombocytopenia), hyperferritinemia (>500 ng/ml), hypertriglyceridemia (>265 mg/dl), and evidence of hemophagocytosis in bone marrow.

Additionally, the HScore, an online diagnostic tool for HLH probability, further supported the diagnosis.

Treatment

The patient was initially treated with empirical antibiotics which were upgraded after blood culture reports and after confirmation of HLH started on intravenous dexamethasone on 29 June 2024. Intravenous immunoglobulin (IVIG) therapy was initiated on 04 July 2024, to control the hyperinflammatory state. Supportive care included blood transfusions for anemia and platelet transfusion, as well as targeted antibiotics for the *Klebsiella pneumoniae* infection and anticholestatic drugs for hyperbilirubinemia.

Outcome

The patient responded favorably to the treatment, with rapid resolution of fever, improvement in pancytopenia, and normalization of inflammatory markers such as ferritin and triglycerides. She showed significant clinical improvement and was discharged with a plan for regular follow-up and further genetic testing (whole-exome sequencing) to rule out primary HLH.

On follow-up, her genetic study revealed primary HLH involving PRF1gene mutation with a homozygous pathogenic variant with autosomal recessive inheritance.

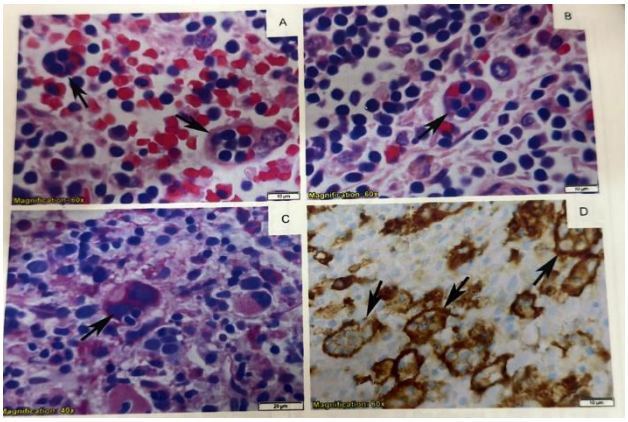

Figure 1 (A-D): Bone marrow aspirate (PAS stain): demonstrates hemophagocytosis and CD163.

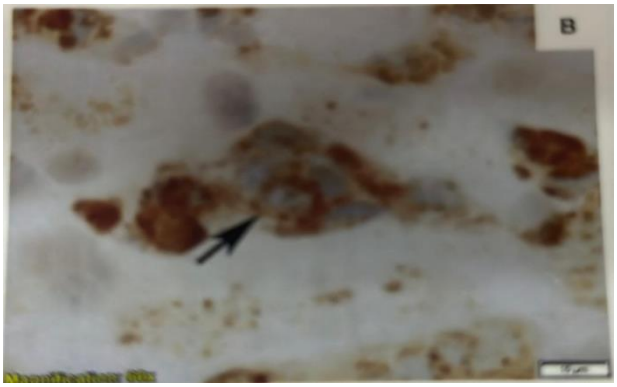

Figure 2: Immunohistochemistry (CD68): highlights activated macrophages in bone marrow tissue, corroborating the histopathological diagnosis.

Table 1: Trend of laboratory investigations of the patient.

Investigations	1/6	2/6	3/6	6/6	14/6	19/6	26/6	28/6	30/6	2/7	3/7	4/7	9/7
HB (gm/dl)	7.6	8.2	8.4	9.1	8.4	8.5		5.7	8.5	8.4		10.3	11.3
HCT (%)	23	25.3	26	28.8	26	26.9			26.7	26.5		33.7	35.4
TLC (cells/ cumm)	2100	3030	4880	2930	3100	3990		1320	1380	3170		3000	5050
Platelet (l/µl)	1.0	1.46	2.25	3.45	0.80	3.03		0.52	0.50	0.75		1.7	3.16
T. bilirubin (mg/dl)	4.06	2.79	2.87	3.27	3.72	2.9	4.09		4.24		2.49		2.22
Direct bilirubin (mg/dl)	3.10	2.19	2.08	2.2	2.81	1.97	2.48		2.97		1.6		1.38
ALT (U/l)	119	71		45	74	98			41		87		
AST (U/l)	74	51	55	32	54		55		109		58		
CRP	12.06					2.02	42.37						0.10
APTT (sec)	26.8	29.0		31.7			45.0				39.9		
PT (sec)	16.1	19.6		13.7			13.6				13.5		
Investigations				**Result**					**Normal values**				
LDH (U/l)				483					1200-300				
Ferritin (ng/ml)				1200					10-291				
Triglycerides (mg/dl)				473					<150				
Fibrinogen (mg/dl)				83					180-350				

DISCUSSION

HLH is a rare hyperinflammatory disorder caused by uncontrolled activation of macrophages, cytotoxic T cells, and natural killer cells. It can be broadly classified into primary (familial) HLH, associated with genetic mutations, and secondary HLH, which occurs due to triggers such as infections, malignancies, or autoimmune disorders.[8,9] This case highlights secondary HLH triggered by *Klebsiella pneumoniae* infection, emphasizing the challenges in diagnosing and managing this potentially fatal condition.

The clinical presentation of HLH is often non-specific, making it difficult to distinguish from other hyperinflammatory states such as severe sepsis or macrophage activation syndrome (MAS). In this case, the patient presented with persistent fever, hepatosplenomegaly, pancytopenia, and elevated inflammatory markers such as ferritin and triglycerides, which are hallmark features of HLH.[10] Bone marrow aspiration further confirmed hemophagocytosis, a pathological hallmark of this syndrome.

The diagnosis of HLH was established using the HLH-2009 diagnostic criteria, which require at least five of eight criteria to be met. In this patient, six criteria were fulfilled, including fever, cytopenias, hepatosplenomegaly, hyperferritinemia, hypertriglyceridemia, and hemophagocytosis in bone marrow. These findings were supplemented by the HScore, which further supported the likelihood of HLH.[11] Importantly, the absence of findings suggestive of malignancy or autoimmune disease and the presence of *Klebsiella pneumoniae* infection considered this as a case of secondary HLH initially.

The underlying pathophysiology of secondary HLH involves excessive cytokine release, particularly of tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ), which drive macrophage activation and hemophagocytosis.[12] This hyperinflammatory state also accounts for elevated ferritin levels, hypertriglyceridemia, and reduced fibrinogen due to cytokine-mediated suppression of lipoprotein lipase and plasminogen activator release, respectively.[13]

Treatment for HLH focuses on controlling hyperinflammation and addressing the underlying trigger. The patient in this case was managed according to HLH-2004 therapeutic guidelines, which recommend the use of dexamethasone and IVIG for immunosuppression and modulation of cytokine release.[14] Empiric antibiotic therapy effectively addressed the bacterial trigger, *Klebsiella pneumoniae*. Early intervention resulted in clinical improvement, including resolution of fever, recovery of cytopenias, and normalization of ferritin and other inflammatory markers. This underscores the importance of timely recognition and initiation of therapy in improving outcomes in HLH.[15]

Genetic testing is essential in cases of secondary HLH, particularly in children from consanguineous families, to identify potential underlying genetic mutations associated with primary HLH. Other significant history in this case was the death of a sibling due to undiagnosed fibril illness complicated with jaundice and encephalopathy. This prompted us to investigate her for primary HLH and hence whole-exome sequencing was done for this patient to evaluate for familial HLH-related gene defects, which may predispose to recurrent episodes of hyperinflammation.[16]

This case demonstrates the need for heightened clinical suspicion for HLH in febrile illnesses with atypical laboratory findings. It also highlights the utility of diagnostic tools such as the HLH-2009 criteria and HScore in confirming the diagnosis and guiding management decisions. Lastly, multidisciplinary care involving pediatricians, hematologists, and infectious disease specialists is critical to optimizing outcomes in HLH.

Diagnosis

The diagnosis of HLH in this case was established based on the HLH-2009 diagnostic criteria, which require at least five of eight specific clinical, laboratory, or histopathological findings to confirm the condition. The 9-year-old patient in this case fulfilled six of the eight criteria, ensuring a definitive diagnosis.

Clinical and laboratory findings

Fever

Persistent high-grade fever exceeding 38.5°C was one of the prominent clinical features observed.

Hepatosplenomegaly

Physical examination revealed both hepatomegaly and splenomegaly, consistent with systemic inflammation.

Cytopenias

The patient exhibited pancytopenia, characterized by decreased hemoglobin (7.5 g/dl), leukopenia (white blood cells at 2,400/µl), and thrombocytopenia (platelets at 80,000/µl), fulfilling the criteria of at least two-lineage cytopenias.

Hyperferritinemia

Ferritin levels were significantly elevated at 18,500 ng/ml, far exceeding the diagnostic threshold of 500 ng/ml, indicating excessive macrophage activation.

Hypertriglyceridemia and hypofibrinogenemia

Laboratory results demonstrated elevated triglycerides (450 mg/dl) and reduced fibrinogen (1.2 g/l), consistent with the metabolic abnormalities associated with HLH.

Hemophagocytosis

Bone marrow aspiration from the posterior superior iliac spine revealed hemophagocytosis in a normocellular marrow, a key histological hallmark of HLH.

Differential diagnosis

Differentiating HLH from mimics such as severe sepsis, malignancy-associated hemophagocytic syndromes, and macrophage activation syndrome (MAS) was critical.

The presence of hyperferritinemia, cytopenias, and hemopha-gocytosis, along with the absence of malignancy and autoimmune markers, supported the diagnosis of HLH rather than its mimics.

Diagnostic tools

Bone marrow examination demonstrated extensive hemophagocytosis (refer to the PAS-stained and immunostained slides in the presentation), confirming excessive macrophage activation.

HLH-2009 diagnostic criteria provided a structured framework, allowing for a definitive diagnosis.

HScore

This online diagnostic tool reinforced the diagnosis, yielding a high probability of HLH based on clinical and laboratory findings.

Trigger identification

Blood culture identified *Klebsiella pneumoniae* as the underlying infectious trigger, ruling out other common pathogens such as HIV, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and dengue, enteric fever, malaria, leptospira, rickettsial, through targeted serologic and PCR-based testing.

In summary, the diagnosis of secondary HLH in this patient was confirmed through a combination of clinical features, laboratory abnormalities, and histopathological evidence. The identification of *Klebsiella pneumoniae* as the infectious trigger further substantiated the diagnosis and guided targeted treatment. This case underscores the importance of adhering to structured diagnostic criteria and utilizing adjunctive tools such as the HScore in evaluating suspected cases of HLH.

Clinical message

HLH is a rare but severe hyperinflammatory condition that poses significant diagnostic and therapeutic challenges due to its overlapping features with sepsis, malignancies, and other systemic inflammatory syndromes. This case highlights several key clinical messages for the timely recognition and management of HLH.

High index of suspicion

HLH should be considered in patients presenting with persistent high-grade fever, hepatosplenomegaly, and pancytopenia, particularly when laboratory findings reveal hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia.

Role of diagnostic criteria

The HLH-2009 diagnostic guidelines are critical in systematically evaluating suspected cases. Fulfilling five of the eight diagnostic criteria enables early and accurate diagnosis, allowing clinicians to initiate appropriate therapy without delay.

Importance of identifying triggers

Secondary HLH often results from infections, malignancies, or autoimmune disorders. Thorough infectious workups, as demonstrated in this case, are essential to identify and address the underlying trigger, such as *Klebsiella pneumoniae* in this instance.

Timely intervention

Prompt initiation of immunosuppressive therapy, including dexamethasone and intravenous immunoglobulin (IVIG), can control the hyperinflammatory state and prevent multi-organ failure. Supportive measures, including blood product transfusions and antimicrobial therapy, play a pivotal role in optimizing outcomes.

Genetic evaluation in pediatric HLH

In children, especially those from consanguineous families, genetic testing is essential to rule out primary HLH and guide long-term management strategies.

This case underscores the importance of a multidisciplinary approach, combining clinical expertise, diagnostic tools, and evidence-based treatment protocols, in successfully managing HLH and improving patient outcomes. Early recognition and intervention remain the cornerstones of effective care for this potentially fatal condition.

CONCLUSION

HLH is a rare but life-threatening hyperinflammatory syndrome that requires a high index of clinical suspicion for timely diagnosis and treatment. This case illustrates the importance of recognizing HLH in patients with persistent fever, pancytopenia, hepatosplenomegaly, and hyperferritinemia. The use of the HLH-2009 diagnostic criteria was instrumental in confirming the diagnosis, while bone marrow examination provided histopathological evidence of hemophagocytosis.

The identification of *Klebsiella pneumoniae* as the underlying trigger emphasizes the necessity of conducting thorough infectious workups in suspected cases of secondary HLH. Prompt initiation of treatment, including dexamethasone and IVIG, successfully controlled the hyperinflammatory state, resulting in significant clinical and laboratory improvement. Supportive care with blood transfusions and targeted antibiotic therapy further contributed to the positive outcome. This case highlights the critical role of early recognition and multidisciplinary management in improving outcomes for HLH patients. It also underscores the need for further genetic evaluation in pediatric cases, particularly in individuals from consanguineous families, to rule out underlying genetic mutations associated with primary HLH.

In conclusion, this case reinforces the importance of integrating clinical findings, diagnostic criteria, and supportive tools such as the HScore in diagnosing HLH. It further demonstrates the effectiveness of evidence-based treatment protocols in achieving favorable outcomes for this severe and complex condition.

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