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SECONDARY HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS – A HYPERINFLAMMATORY SYNDROME UNMASKED BY BONE MARROW HEMOPHAGOCYTOSIS

Pathology

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ABSTRACT

Hemophagocytic lymphohistiocytosis (HLH) is a rare but life-threatening hyperinflammatory syndrome characterized by uncontrolled activation of macrophages and cytotoxic T-cells, resulting in excessive cytokine production and multiorgan dysfunction. HLH may occur as a primary (familial) condition due to genetic defects or more commonly as secondary HLH triggered by infections, malignancies, autoimmune diseases, or immunodeficiency states. Early diagnosis remains challenging because of its nonspecific clinical presentation, but prompt recognition is critical to prevent fatal outcomes. HLH is an aggressive and potentially fatal syndrome that requires a high index of clinical suspicion for early diagnosis. Bone marrow examination plays a crucial supportive role in identifying hemophagocytosis in patients presenting with unexplained fever and cytopenia. Early recognition using HLH-2004 criteria and timely initiation of appropriate therapy are essential to prevent rapid disease progression and multiorgan failure.

KEYWORDS

Hemophagocytic Lymphohistiocytosis (HLH), Secondary HLH, Hemophagocytosis, Pancytopenia, Hyperferritinemia, Bone Marrow Aspiration

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal hyperinflammatory syndrome characterized by excessive activation of immune cells, particularly macrophages and cytotoxic T-lymphocytes, leading to uncontrolled systemic inflammation. This dysregulated immune response results in excessive cytokine production, commonly referred to as a cytokine storm, which can rapidly lead to multiorgan dysfunction and high mortality if not diagnosed early.

HLH is broadly classified into two forms:

Primary (Familial) HLH:

This form is caused by inherited genetic mutations affecting cytotoxic pathways, particularly involving genes responsible for perforin-mediated cytolysis such as PRF1, UNC13D, STX11, and STXBP2. It typically presents in infancy or early childhood.

2. Secondary (Acquired) HLH: Secondary HLH occurs as a complication of underlying conditions including:

- Severe infections (viral, bacterial, fungal, or parasitic)
- Hematological malignancies (especially lymphomas)
- Autoimmune diseases such as Systemic Lupus Erythematosus
- Immunodeficiency states
- Metabolic disorders

Infection-associated HLH is particularly common in tropical and Asian regions. Viral infections such as Epstein–Barr virus (EBV), cytomegalovirus (CMV), and dengue virus are well-recognized triggers.Because clinical manifestations are often nonspecific, early diagnosis remains challenging. Bone marrow examination demonstrating hemophagocytosis plays a key supportive role in establishing the diagnosis.

RESULTS

Case Details

A 35-year-old male presented to the hospital with complaints of:

- Persistent high-grade fever for 20 days
- Chills and rigors
- Progressive generalized weakness
- Jaundice

On clinical examination, the patient was found to have:

- Hepatomegaly
- Splenomegaly
- Pallor
- Signs of systemic inflammation

Initial laboratory investigations revealed:

- Bicytopenia (reduction in two blood cell lines), which later progressed to pancytopenia
- Elevated inflammatory markers
- Hypertriglyceridemia – 705 mg/dL
- Markedly elevated serum ferritin levels (>2000 ng/mL)

Additional findings included deranged liver function tests and elevated lactate dehydrogenase levels, suggestive of systemic inflammatory response and tissue damage. Based on the constellation of clinical findings and laboratory abnormalities, a suspicion of hemophagocytic lymphohistiocytosis was raised and further evaluation was performed.

Microscopy / Bone Marrow Findings

Bone marrow aspiration and examination were carried out to evaluate the cause of pancytopenia.

Microscopic examination revealed:

- Hypocellular marrow
- Scant cellular trails
- Numerous foamy histiocytes
- Prominent hemophagocytosis

The histiocytes were seen actively engulfing:

- Erythrocytes
- Leukocytes
- Platelets

Importantly, the following findings were absent:

- No evidence of blast cells
- No granulomas
- No hemoparasites

These findings strongly supported the diagnosis of secondary hemophagocytic lymphohistiocytosis.

The clinical presentation, laboratory findings, and bone marrow morphology collectively fulfilled the HLH-2004 diagnostic criteria.

Diagnosis

Secondary Hemophagocytic Lymphohistiocytosis (HLH).The

diagnosis was established using the HLH-2004 diagnostic guidelines, which require either:

- A molecular diagnosis consistent with HLH,
- Five out of eight clinical and laboratory criteria.

The HLH-2004 criteria include:

1. Fever
2. Splenomegaly
3. Cytopenias affecting ≥2 cell lines
4. Hypertriglyceridemia and/or hypofibrinogenemia
5. Hemophagocytosis in bone marrow, spleen, or lymph nodes
6. Low or absent NK-cell activity
7. Hyperferritinemia (>500 ng/mL)
8. Elevated soluble CD25 (IL-2 receptor)

In this case, several criteria were fulfilled, including:

- Fever
- Cytopenia
- Hypertriglyceridemia
- Hyperferritinemia
- Bone marrow hemophagocytosis
- Hepatosplenomegaly

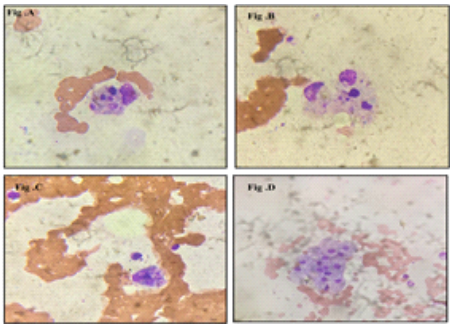

Figure: Microscopic examination

DISCUSSION

HLH represents a severe hyperinflammatory immune dysregulation syndrome caused by ineffective cytotoxic activity of natural killer (NK) cells and cytotoxic T lymphocytes.

Due to impaired cytotoxic function, antigen-presenting cells remain persistently activated, leading to uncontrolled macrophage activation and excessive cytokine release. The resulting hypercytokinemia includes elevated levels of:

- Interferon-
- Tumor necrosis factor-α
- Interleukin-6
- Interleukin-10

This cytokine storm causes:

- Tissue damage
- Bone marrow suppression
- Multiorgan dysfunction

Clinically, patients often present with:

- Persistent fever
- Cytopenias
- Hepatosplenomegaly
- Liver dysfunction
- Coagulopathy
- Hyperferritinemia

Among laboratory markers, serum ferritin levels are particularly important, as extremely high levels (>10,000 ng/mL) are highly suggestive of HLH.

Bone marrow examination is not always mandatory for diagnosis but provides strong morphological evidence when hemophagocytosis is identified.

Early recognition and treatment are crucial because HLH can rapidly progress to multiorgan failure and death. Standard treatment protocols include:

- Immunosuppressive therapy
- Corticosteroids
- Etoposide-based regimens
- Treatment of the underlying trigger

CONCLUSION

Hemophagocytic lymphohistiocytosis is a life-threatening hyperinflammatory condition that requires a high index of clinical suspicion for timely diagnosis.

This case highlights the importance of integrating:

- Clinical presentation
- Laboratory parameters
- Bone marrow findings

for early recognition of secondary HLH.

Bone marrow examination remains a valuable diagnostic tool in patients presenting with unexplained fever and cytopenia. Early identification using the HLH-2004 criteria and prompt initiation of therapy are essential to prevent rapid disease progression and multiorgan failure.

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