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# A CLINICOPATHOLOGICAL EVALUATION: A RARE CASE REPORT OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS SECONDARY TO MULTIPLE INFECTIONS.

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## ABSTRACT

HLH is a rapidly progressive and potentially fatal disorder if left undiagnosed. HLH is a disorder with extensive hemophagocytosis characterized by uncontrolled proliferation of NK cells and T cells that result in immune system activation and cytokine deregulation accompanied by the presence of macrophages at various tissue sites the consequence of which is tissue damage and progressive multiple-organ failure. Missed or late diagnosis is believed to be a major cause of high mortality. We report a case of 23 years male who presented with complaints of high-grade fever with chills, headache, yellowish discoloration of urine and sclera for 7 days with the positivity of P. falciparum (PF Gametes and PF antigen-positive) infection. Blood inhouse investigations suggested bicytopenia; HBsAg, Dengue IgM positivity by ELISA; elevated levels of ALT, total bilirubin, IL-6, procalcitonin, CRP, Serum Triglyceride, Serum Ferritin, D-Dimer and S.LDH. USG abdomen suggested hepatosplenomegaly. Bone marrow examination revealed increased phagocytic activity which showed target cells (macrophages) were highlighted by CD 68 on immunohistochemistry. The final diagnosis was determined based on the HLH 2009 criteria. Immediately treatment was started with immunosuppressants resulting in a significant improvement of blood count parameters and the patient's general condition and was discharged after 2 weeks.

**Keywords**: Hemophagocytic Lymphohistiocytosis (HLH), elevated serum ferritin, hepatosplenomegaly, CD68, HLH 2009 criteria, immunosuppressants

**INTRODUCTION:**

Epidemiologic data of HLH in the adult population is limited. HLH can be caused either by certain underlying genetic diseases (familial HLH) or may also occur due to triggers in patients with no known inherited disorder (acquired HLH). Due to the life threatening nature of the disease, early diagnosis and initiation of immunosuppressive therapy are extremely important. This case was very complicated based on the constellation of clinical manifestations and laboratory parameters, which made prompt diagnosis difficult. The present study aimed to assess the disease course with multiple infections and the outcome of this entity. Furthermore, the literature on the subject has been scarce.

**MATERIAL AND METHOD:**

The case report was conducted in the Haematology laboratory of the institute. Bone marrow examination was done for clinical suspicion of hemophagocytosis Lymphohistiocytosis. Demographic information, clinical characteristics, diagnostic impressions and laboratory values were collected before the procedure. Bone marrow biopsy and aspiration were done under aseptic precaution. Laboratory biomarkers, peripheral smear, bone marrow examination and immunohistochemistry findings were analyzed. The final diagnosis was determined based on the HLH 2009 criteria in conjunction with the overall clinical picture.

**CASE REPORT:**

We report a case of 23 years old male who came with complains of high-grade fever with chills, headache, yellowish discoloration of urine and sclera for the last 7 days with the positivity of P. falciparum (PF Gametes and PF antigen-positive) infection. He had no significant past history or family history. On examination, abdominal distention was present. Blood and radiological investigations were done inhouse which were following **(Table 1)**. Initially, the patient was treated with antimalarials and supportive therapy. Despite all these measures, his course was unresponsive and complicated by fever along with prolonged severe bicytopenia. The patient was advised for bone marrow examination to evaluate phagocytic activity.

**Bone marrow Aspiration and biopsy findings: (Tables 2 & 3)**

Cellularity – Mildly hypocellular for the age of the patient.

Mild erythroid hyperplasia with normal maturation.

Smear showed increased phagocytic activity with macrophages engulfing platelets, neutrophils, nucleated RBCs. Many macrophages showed brownish-black pigments (suggest malarial pigments), hemosiderin pigments, foamy cytoplasm, and cellular debris. **(Figures 1-4)**

Target cells (macrophages) were highlighted by CD 68. **(Figure 5)**

In support with peripheral smear, laboratory biomarkers, bone marrow and immunohistochemistry findings the patient was diagnosed with **Secondary Hemophagocytic Lymphohistiocytosis.**

Secondary HLH may be due to Plasmodium falciparum &/or dengue &/or Hepatitis B.

He was started on HLH therapy with immunosuppressant and supportive management. The patient responded to

immunosuppressants resulting in a significant improvement of blood count parameters and the patient's general condition and was discharged after 2 weeks.

**DISCUSSION:**

HLH is a life-threatening condition of immune hyper-activation and divided into primary HLH, which is an autosomal recessive condition, caused by mutations impairing the cytotoxic function of NK cells and cytotoxic T lymphocytes and in association with the immune deficiencies Chédiak Higashi syndrome (CHS), Griscelli syndrome (GS) and X-linked lymphoproliferative syndrome (XLP); and secondary HLH occurs sporadically. Secondary HLH is the more frequent presentation in adults and frequently identified triggers include hematologic infections, malignancies and autoimmune conditions. Mortality in secondary HLH varies based on the underlying conditions. Based on some studies, more than 80% of HLH are associated with malignancy and around 8% when associated with juvenile idiopathic arthritis. Incidence in the adult population is less clear.[1]

The present study observed that hemophagocytosis was associated with infections including viral and parasitic infections. Dhote R et al reported a prevalence of viral infections (29%), other infections (20%), malignancies (27%), rheumatologic disorders (7%) and immune deficiency syndromes (6%).[2]

Malaria as a cause of secondary HLH is rare. We studied the related literature, and very few cases have been reported. The types of malarial parasites that cause secondary HLH are P. falciparum and P. vivax, with P. falciparum accounting for most of these cases. The pathogenesis is unclear but may be related to immune dysfunction caused by falciparum malaria, which still needs further study. [3]

HLH in dengue infection remains a diagnostic challenge and can be misdiagnosed as sepsis because of the nonspecific, overlapping clinical features. Most of the patients with secondary HLH have features like fever, hypotension, shock and multisystem organ failure which are also common in severe dengue. Hyperferritinemia observed in patients with dengue infection is suggestive of highly active disease with an increased risk of hyper inflammation and coagulation disturbances.[4] In such scenarios, NK cell activity and soluble CD4 counts are two tests that will help us differentiate these conditions from HLH as their sensitivity in HLH is 100%. [5]

Our patient also had a Hepatitis B infection. In the literature review, HLH was attributed to HBV in 13 cases.[6] This is the first reported case of HLH attributed to HBV, malaria and dengue coinfections to the best of our knowledge.

Criteria for the diagnosis of HLH proposed by the HLH 2009 criteria include clinical, laboratory, and histopathologic features. The most prominent clinical diagnostic criteria evident in our patient included fever, hepatomegaly, splenomegaly and laboratory abnormalities noted in our patient are bicytopenia with hyperbilirubinemia, the elevation of lactate dehydrogenase, hypertriglyceridemia and marked elevation of ferritin. Serum fibrinogen is typically low and increases hemophagocytosis on bone marrow findings.

Hemophagocytosis cannot be used as a necessary condition to exclude or diagnose HLH. The sensitivity of hemophagocytosis in the diagnosis of HLH is approximately 60%. The sensitivity of ferritin > 500 µg/L in the diagnosis of HLH is 84%. sCD25 is the most useful marker of inflammation. [7]

HLH is a life-threatening condition and only pathogen directed therapy is usually not sufficient to control severe hyper-inflammation in HLH.[8] It should be started in clinically suspected cases even when results of a few diagnostic criteria are pending.

**CONCLUSION:**

We report a case with a rare presentation of secondary hemophagocytic lymphohistiocytosis with multiple infections. Clinicians must possess a high index of suspicion for diagnosing HLH amongst patients presenting with fever and cytopenia especially with underlying infection, malignancy or immunosuppressive states. Early diagnosis of the primary disease along with timely intervention and a multidisciplinary approach can help patients achieve a satisfactory outcome.

**Table 1: Inhouse investigation findings**

| Investigations | Value | Reference range |
|---|---|---|
| **CBC** | | |
| Hb | 7.2 gm/dl | 14-16 gm/dl |
| HCT | 20.6% | 41-50% |
| RC | 0.5% | 0.5-1.5% |
| TLC | 5.06 x $10^3$/cu.mm | 3.5-10 x $10^3$/cu.mm |
| Platelet count | 81 x $10^3$/cu.mm | 150-400 x $10^3$/cu.mm |
| N/L/E/M | 67/30/02/01 | |
| Peripheral smear: | Predominantly Normocytic Normochromic, few target cells and occasional nRBCs. Toxic granules in neutrophils seen. | |
| **LFT** | | |
| ALT | 82 U/L | <45 U/L |
| Total Bilirubin | 32 mg/dl | 0-1 mg/dl |
| Direct Bilirubin | 25 mg/dl | Upto 3 mg/dl |
| Indirect Bilirubin | 07 mg/dl | 0.1-1 mg/dl |
| **RFT** | | |
| S.Creatinine | 8 mg/dl | 0.9-1.3 mg/dl |
| Blood Urea | 26 mg/dl | 14-43 mg/dl |
| **Other markers** | | |
| Triglyceride | 261 mg/dl | <150 mg/dl |
| S.Ferritin | 16574 ng/ml | 22-322 ng/ml |
| S.Procalcitonin | 9.29 ng/ml | <0.0.5 ng/ml |
| S.LDH | 1456 U/L | 85-227 U/L |
| CRP | 104.8 mg/dl | <3 mg/dl |
| IL-6 | 22.9 pg/ml | <4.4 pg/ml |
| **Microbiology** | | |
| HBsAg | Positive | |
| Dengue IgM (ELISA) | Positive | |
| **USG Abdomen** | Hepatomegaly (18 cm) with normal echo texture | |
| | Splenomegaly (15.8 cm) with normal echo texture | |

**Table 2: Bone marrow aspiration findings**

| | |
|---|---|
| Site: | Left posterior superior iliac spine |
| Marrow particle: | Grossly appreciated |
| Cellularity: | Mildly hypocellular for the age of the patient |
| Erythropoiesis: | Mildly erythroid hyperplasia with normal maturation |
| Myelopoiesis: | Normal with normal maturation |
| Megakaryopoiesis: | Normal with normal maturation, Normal with normal maturation, 3-5 / LPF and adequate in number. Smears showed increased phagocytic activity with macrophages engulfing platelets, neutrophils, nucleated RBCs. Many macrophages showed brownish black pigments (suggests malarial pigments) along with hemosiderin pigments, Foamy cytoplasm and contain cellular debris. |
| Iron store: | +5 |

**Table 3: Bone marrow Biopsy findings**

| | |
|---|---|
| Site: | Left posterior superior iliac spine |
| Cellularity: | Mildly hypocellular for the age of the patient |
| Erythropoiesis: | Mildly erythroid hyperplasia with normal maturation |
| Myelopoiesis: | Normal with normal maturation |
| Megakaryopoiesis: | Normal with normal maturation.<br>The sections showed an increased phagocytic activity with macrophages engulfing platelets, neutrophils, nucleated RBCs. Many macrophages show brownish black pigments (suggests malarial pigments) along with hemosiderin pigments, Foamy cytoplasm and contain cellular debris. |
| Immunohistochemistry: | Target cells (macrophages) are highlighted by CD 68. |

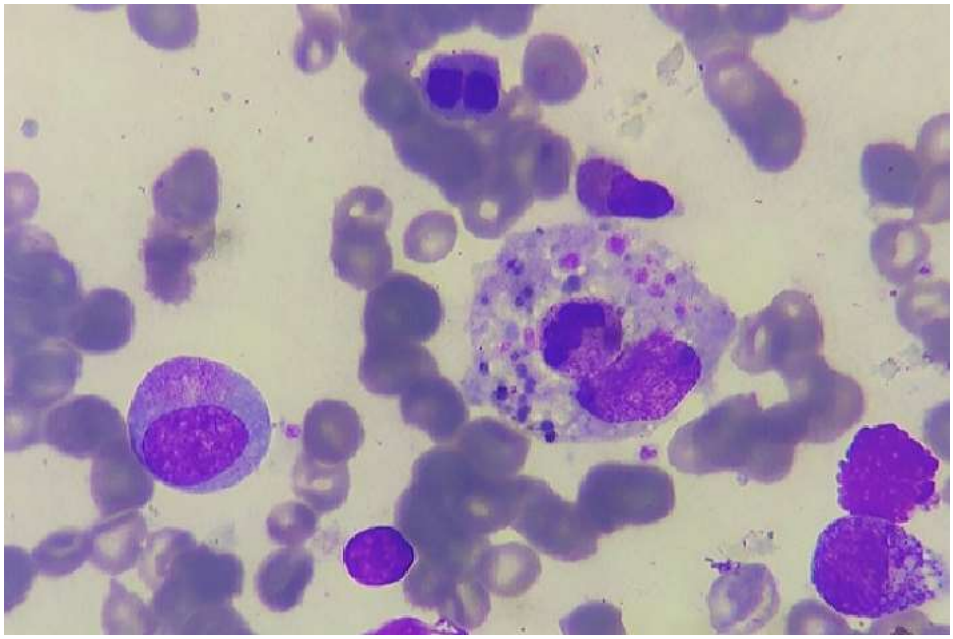

**Fig 1: Macrophages showing cellular debris. (Giemsa, 100x)**

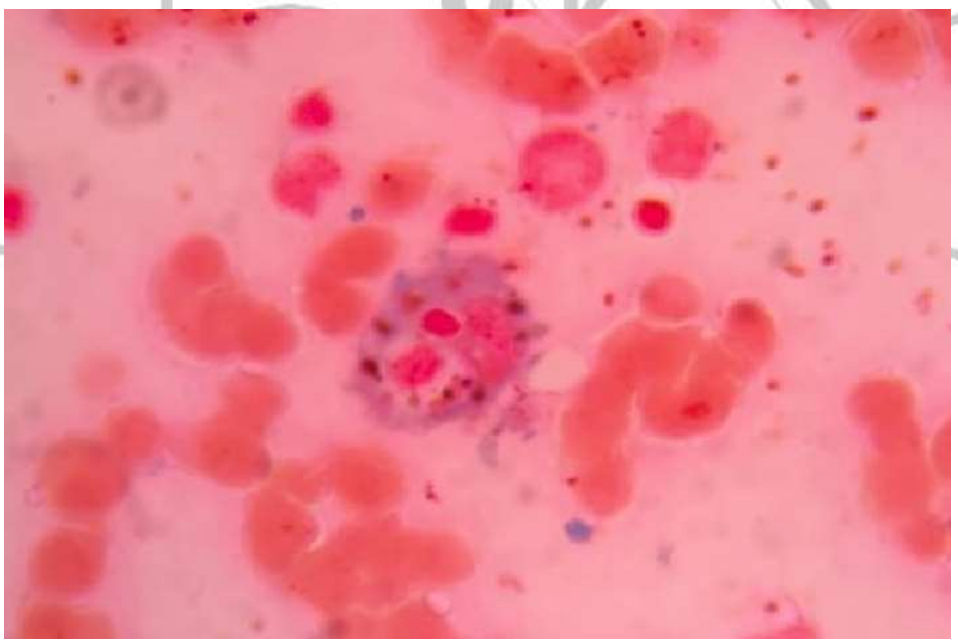

**Fig 2: Macrophages containing hemosiderin pigments, foamy cytoplasm, and cellular debris. (Prussian Blue, 100x)**

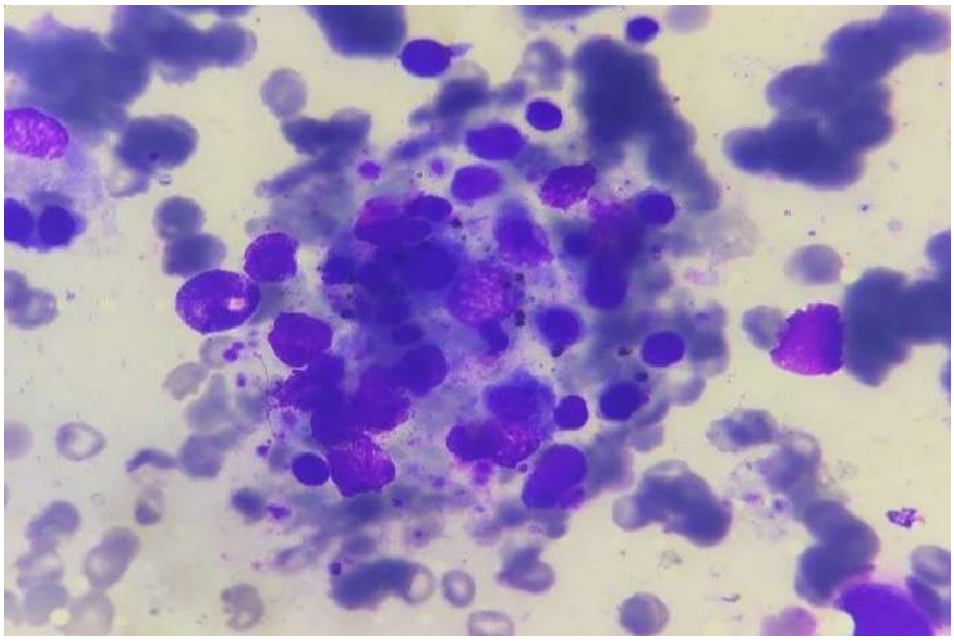

**Fig 3: Increase macrophage activity with macrophages engulfing platelets, neutrophils, nucleated RBCs. (Geimsa, 100x)**

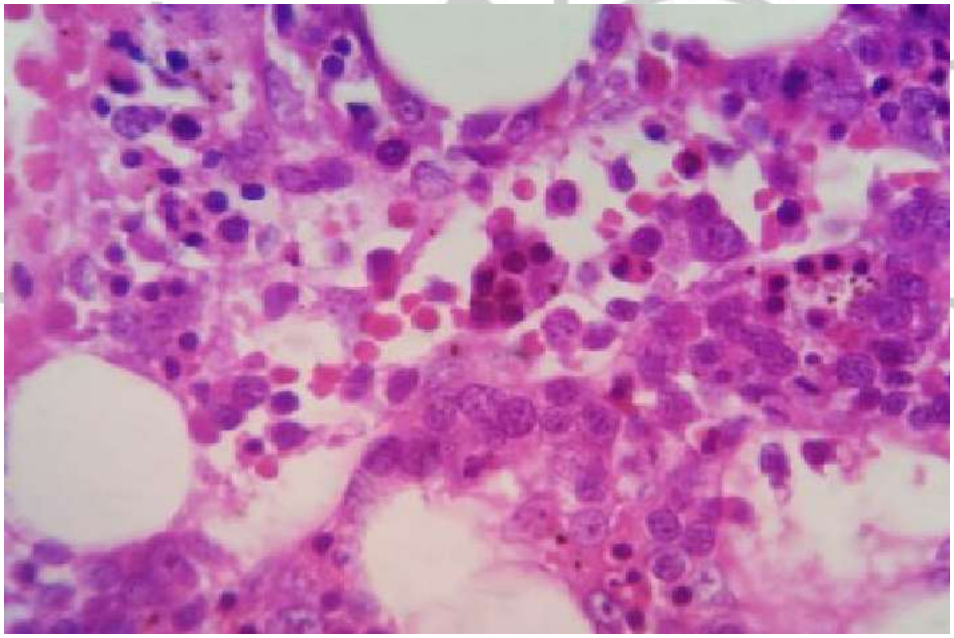

**Fig 4: Bone marrow biopsy showing macrophage engulfed nucleated RBCs. (H&E, 100x)**

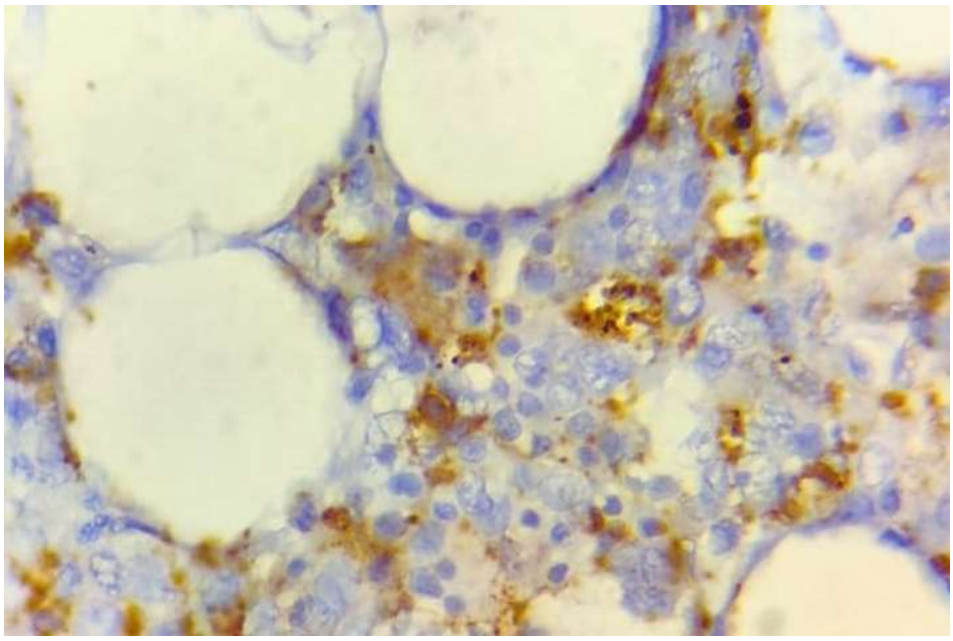

**Fig 5: Target cells (macrophages) are highlighted by CD 68. (IHC, 100x)**

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**CONFLICT OF INTEREST**

Not applicable

**Reference:**

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