# Idiopathic Hemophagocytic lymphohistiocytosis (HLH) in an 8-Month-Old child : A case report

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**Abstract**

Hemophagocytic lymphohistiocytosis (HLH) has varied clinical presentations. Prompt recognition and initiation of appropriate treatment can prevent cytokine storm and fatal outcomes. We report a case of an 8-month-old male child presented with non-specific clinical complaints and hyperferritinemia and was successfully treated with dexamethasone.

**Keywords:** HLH, Hemophagocytic lymphohistiocytosis, hyperferritinemia, dexamethasone

## 1 Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an uncommon, potentially fatal hyperinflammatory disorder characterized by uncontrolled activation of cytotoxic T-lymphocytes (CTLs), natural killer (NK) cells, and macrophages resulting in hypercytokinemia and immune-mediated injury of multiple organ systems [6, 20]. It mostly affects infants from birth to 18 months of age but is also observed in children and adults of all ages [11]. In Europe and Japan, the incidence of HLH has been estimated 1.2 per million children per year [2, 11, 12]. While in the USA, the prevalence of HLH was calculated 1 in 100,000 [2, 13]. In some cases, the cause of HLH remains obscure. HLH can present as the primary syndrome or occur secondary to a variety of conditions such as infections, malignancies, autoimmune and autoinflammatory disorders [2, 16]. Early recognition and initiation of specific management of HLH are often challenging as both the subtypes share similar clinical and laboratory findings like persistent high fever, hepatosplenomegaly, petechial/purpuric rash, progressive cytopenia, hypertriglyceridemia, hypofibrinogenemia, and hyperferritinemia often with multi-organ involvement [7, 17, 19]. A serum ferritin level of >10000 ng/mL is a strong indicator of HLH[7, 15]. A serum ferritin level of >3000 ng/mL implies an increased risk for both receipt of critical care and subsequent death [21]. We hereby discuss a case of an 8-month-old male child presented with persistent high fever, erythematous body rash, generalized body swelling, and oliguria with laboratory findings in terms of bicytopenia, hypertriglyceridemia, hypofibrinogenemia and hyperferritinemia with serum ferritin level > 20000ng/mL, successfully managed with eight weeks of dexamethasone administration.

## 2 Case description

An 8-month-old male child was presented with fever for 20 days, generalized body rash for 16 days, generalized body swelling, and decreased urine output for seven days, with multiple visits in other hospitals. After having excessive irritability for about a week, the child developed acute onset of fever with a maximum documented temperature of 40 degrees Celsius, not associated with chills and rigor, no diurnal variation, relieved on antipyretics. After four days of fever, he developed eye redness with no eye discharge, followed by the development of a rash on his face which progressively increased to involve the whole body. He was treated with oral azithromycin and cefpodoxime, which didn't relieve his symptoms. He was admitted to a tertiary-level hospital, where he received intravenous piperacillin/tazobactam (ZOSYN), amikacin, doxycycline, and intravenous hydrocortisone for two days. He got discharged after two days as his symptoms started decreasing. However, his fever didn't subside, and he started passing greenish-yellow semisolid stool almost 5-6 times a day, non-mucoid, non-blood stained, and not associated with pain abdomen. He then developed generalized body swelling starting from the abdomen, along with decreased urine output, for which he was admitted to a private hospital for 10 days. The laboratory findings during the period of hospital stay are summarized in table 1.

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| Parameter | Reference range | Day 1 | Day 3 | Day 5 | Day 7 | Day 9 | Day 10 |
|---|---|---|---|---|---|---|---|
| Hemoglobin (gm/dL) | 12 - 15 | 9.2 | 9.5 | 11.1 | 8.7 | 7.7 | 8.1 |
| RBC count ($10^3$ per $\mu$L) | 4.5 - 5.5 | - | - | - | 3.53 | 3.23 | 3.39 |
| Hematocrit (%) | 40 - 50 | - | - | - | 23.8 | 22.2 | 22.8 |
| TLC (100 cells per $mm^3$) | 40 - 110 | 147 | 65 | 67 | 149.9 | 215 | 164 |
| Neutrophils (%) | 40 - 60 | 74 | 73 | 48 | - | - | - |
| Lymphocyte (%) | 20 - 45 | 21 | 24 | 51 | 54.3 | 19.80 | 16.6 |
| AST (SGOT) (U/L) | 5 - 40 | - | - | 5578 | 953 | 848 | - |
| ALT (SGPT) (U/L) | 5 - 45 | - | - | 2446 | 1324 | 1022 | - |
| G-GT (U/L) | 15 - 73 | - | - | - | 1247 | 721 | - |
| Total protein (gm/dL) | 6 - 8 | - | - | - | 4.6 | 4.7 | - |
| Albumin (gm/dL) | 3.5 - 5 | - | - | - | 2.5 | 2.5 | - |
| LDH - Total (U/L) | 200 - 420 | - | - | - | - | - | 2617 |
| Ferritin (ng/mL) | 21 - 274 | - | - | - | - | - | $> 1000$ |
| ESR (mm/hour) | 0 - 10 | - | 45 | - | - | - | 35 |
| Serum CRP (mg/L) | 0 - 6 | - | Positive | - | - | - | $> 90$ |

Table 1: Laboratory findings during the clinical course. Abbreviations: RBC, Red blood cells; TLC, Total leukocytes count; AST, Aspartate transaminase; ALT, Alanine aminotransaminase; G-GT, Gamma-glutamyl transferase; LDH, Lactate dehydrogenase; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein.

He was treated with intravenous ZOSYN, amikacin, meropenem, vancomycin and azithromycin. During further workup, his serum LDH and ferritin were noted very high (see table 1), symptoms were not relieving and no specific cause was identified, so he was shifted to another hospital for further workup and management.

At the time of admission for the third time, his vital parameters were recorded as follows: temperature 36.7 degrees Celsius, heart rate 148 bpm, respiratory rate 47/min, and oxygen saturation 95% at room air. His length and weight were 68 cm and 8.4 kg respectively, implying the normal weight-for-length($\geq -2$ to $\leq 2$). General body examination revealed generalized anasarca with erythematous blanchable macular rash all over the body, including palm and soles (non blanching red pin point lesions), signs of pallor, and bilaterally palpable, soft, discrete and non-tender solitary axillary lymph node measuring approximately 2cm×1cm. The abdomen was mildly distended, the umbilicus was central and slit-shaped, and the liver was palpated about 4cm below the right costal margin. However, other general and systemic findings were unremarkable. The child was started on broad spectrum antibiotics, intravenous meropenem and vancomycin, suspecting infection and, hence other investigations were sent to rule out various causes including HLH, as he had very high ferritin level and deranged liver enzymes. Hemogram report showed bicytopenia (hemoglobin 7.7gm/dL, platelets 85000/$mm^3$), elevated total leukocyte count 16,600/$mm^3$, differential leukocyte count N63%,L25%,M5% and E5% with normal renal function test measuring urea 15 mg/dL, creatinine 0.3 mg/dL, Na+ 139.2 mEq/L and K+ 3.69 mEq/L at the time of admission.

## 2.1 Imaging studies and further investigations

Ultrasound of the abdomen revealed mild ascites, hepatosplenomegaly with normal echotexture of the liver. The child was further evaluated with two samples of blood culture and one sample of urine culture which revealed no microbial growth. Echocardiogram(ECHO) showed no coronary artery dilatation or aneurysms. Tests result for Epstein-Barr virus (EBV), Cytomegalovirus (CMV), SARS-CoV-2, Chikungunya, Dengue, Malaria, Scrub typhus, Brucellosis, Leptospirosis were negative. Histopathological report of the erythematous rash showed occasional apoptotic keratinocytes in epidermis and mild spongiosis with mild perivascular chronic inflammation and pigment incontinence in the upper dermis. However, eosinophils/ vasculitis were not identified in the section examined. Also, antinuclear antibody(ANA), antineutrophil cytoplasmic antibody (p-ANCA and c-ANCA), complement 3 (C3) and complement 4(C4) tested negative. Bone marrow aspiration showed occasional hemophagocytosis. However, bone

marrow biopsy revealed normocellular marrow with hematopoietic elements of all three series with no atypical cells. He had elevated ESR 22 mm/hour, raised CRP 66.44mg/L, positive procalcitonin 1.74 ng/mL (reference range: $< 0.15$ ng/mL), elevated serum LDH 2723 U/L, elevated serum triglycerides 331mg/dL(reference range: $< 150$ mg/dL), excessively elevated ferritin 20,337 ng/mL, decreased fibrinogen 130 mg/dL (reference range: 200 - 400 mg/dL), decreased serum zinc 71.38$\mu$g/dL(reference range: 75-291 $\mu$g/dL), highly elevated liver enzymes SGOT/SGPT/ALP 851/446/712 U/L respectively with decreased total protein and serum albumin 4.2 gm/dL and 2.4 gm/dL respectively. Differential diagnosis of HLH was speculated based on the clinical presentations and laboratory findings. Our findings were compared with the 2004-HLH diagnostic criteria [4] (see table 2), and 6 out of 8 criteria were fulfilled so the diagnosis of HLH was made.

| **At least five of the following:** | **Traditional HLH-2004 criteria** | **Our patient** |
|---|---|---|
| Fever | $> 38.5$ | 40 |
| Splenomegaly | + | + |
| Cytopenia affecting atleast two cell lines | | |
| • Hemoglobin | $< 9$ g/dL | 7.7 g/dL |
| • Platelet count | $< 100000/\text{mm}^3$ | $85000/\text{mm}^3$ |
| • Absolute neutrophil count | $< 1000$ b/L | - |
| Hypertriglyceridemia and/or hypofibrinogenemia | | |
| • Triglycerides | $> 265$ mg/dL | 331 mg/dL |
| • Fibrinogen | $< 150$ mg/dL | 130 mg/dL |
| Ferritin | $\geq 500$ ng/mL | 20337 ng/mL |
| Low/absent NK-cell activity | + | ND |
| Hemophagocytosis in bone marrow, spleen, lymph node or liver | + | Occasional |
| Soluble CD25 (soluble IL-2 receptor) | $> 2400$ U/ml | ND |

Table 2: Diagnostic traditional criteria of HLH - 2004 compared to the features of our patient.

To identify the primary or secondary cause of HLH, a panel of molecular genetic tests and other tests were performed and the child was started on intravenous dexamethasone at $10\text{mg/m}^2$ per day following HLH-94 treatment protocol without waiting the arrival of the reports. [1]. The child showed clinical stability within 24 hours and improvement in laboratory findings was observed as shown in figure 1.

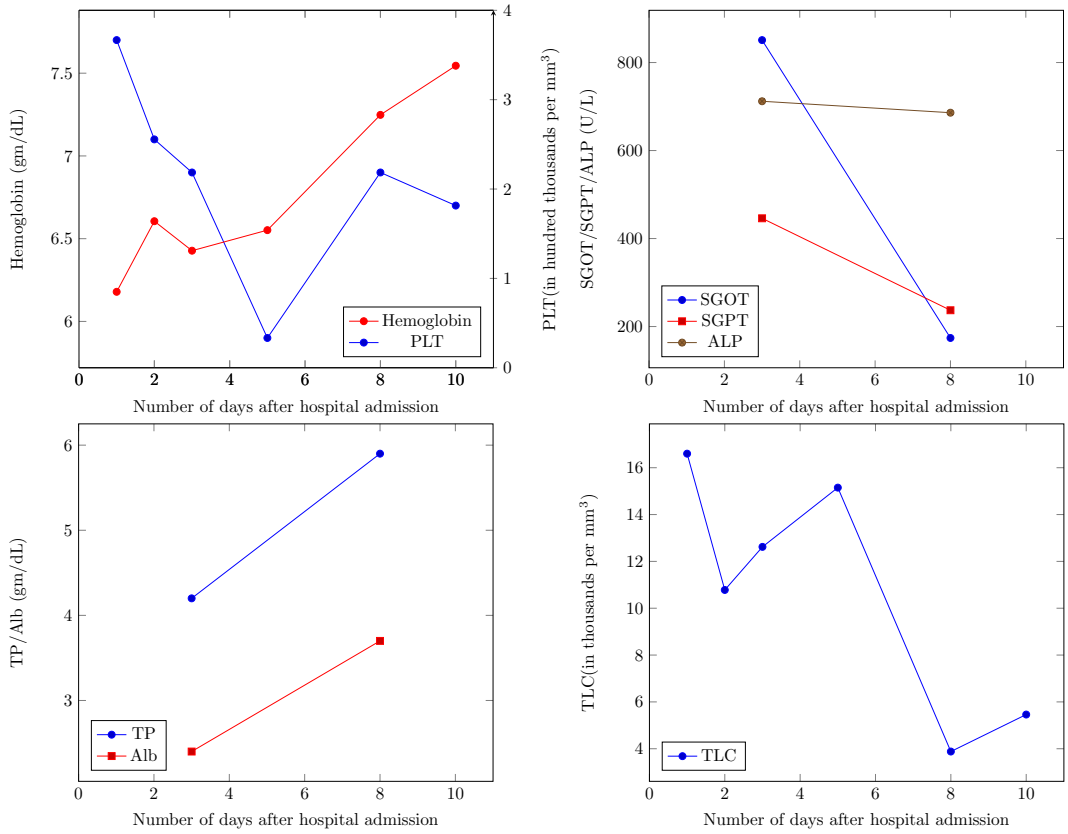


Figure 1: Graphs showing the trend of Hb, PLT, SGOT, SGPT, ALP, TP, Alb and TLC over a period of a few days after the administration of dexamethasone.

# 3 Discussion

HLH is a hyperinflammatory syndrome and one of the most aggressive life-threatening disorders in pediatric hematology. Historically, HLH was classified into two major groups: primary and secondary. Primary HLH is mainly observed in pediatric populations and is caused by mutation in genes regulating granule dependent cytotoxicity of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells [2, 10]. Mutations in nine genes have further subclassified primary HLH into familial HLH Type 1 to 5, HLH associated with various syndromes and HLH associated with X-linked lymphoproliferative diseases[2]. Secondary or acquired HLH is observed in adult population and is associated with several infections [14], malignancies, autoimmune and autoinflammatory disorders [2] as mentioned in table 3..

Recently, the North American Consortium for Histiocytosis suggested broader classification of HLH to include other causes of secondary HLH such as HLH with negative genetic abnormalities and no specific secondary cause, or HLH observed after immune activation (iatrogenic HLH)[3]. Regardless of underlying etiology for HLH, hyperactivity of immune system leads to excessive release of inflammatory mediators including tumor necrosis factor-alpha (TNF-$\alpha$), interleukin (IL-6 and IL-12), interferon gamma (IFN$\gamma$) producing a cytokine storm that leads to excessive macrophage and T-cell activation and subsequently the appearance of clinical features and laboratory findings of HLH contributing to tissue damage and progressive systemic organ failure [2, 18]. On the other hand, NK-cells and CTLs cannot eliminate active macrophages, which causes an imbalance in the immune systems's regulation [22, 5]. HLH also shares various nonspecific clinical and laboratory abnormalities with various conditions like sepsis [5] , malignancies, autoinflammatory disorders making the definitive diagnosis and management often challenging.

The child in our case had all the features consistent with diagnosis of sepsis so initial treatment was initiated with antibiotics. However, culture of blood and urine did not reveal any microbial growth and symptoms didn't relieve with antibiotics so sepsis was excluded. Atypical Kawasaki disease was eliminated as there was no change in lips and oral cavity, absence of cervical lymphadenopathy and no periungual desquamation. ECHO suggested absence of coronary artery dilatation or aneurysms. Normal value of ANA, p-ANCA, c-ANCA, C3 and C4 ruled out the possibility of autoimmune and autoinflammatory disorders. Laboratory investigations revealed anemia, thrombocytopenia, hypofibrinogenemia, hypertriglyceridemia, hyperferritinemia, elevated liver enzymes, elevated

| **Primary HLH** | | | **Secondary HLH** |
|---|---|---|---|
| Subtype | Mutation | Protein | Associated with |
| Familial HLH type 1 | Unknown | Unknown | Infections |
| Familial HLH type 2 | *PRF1* | Perforin | Viral (EBV, CMV, etc.) |
| Familial HLH type 3 | *UNC13D* | Munc13-4 | Bacterial (*Mycobacterium*, etc.) |
| Familial HLH type 4 | *STX11* | Syntaxin-11 | Fungal (*Histoplasma*, etc.) |
| Familial HLH type 5 | *STXBP2* | Munc18-2 | Parasitic (*Leishmania*, etc.) |
| Griscelli syndrome type 2 | *RAB27A* | Rab27a | Malignancy |
| Chediak-Higashi syndrome | *LYST* | LYST | (Lymphoma, leukaemia, etc.) |
| Hermansky-Pudlak syndrome type 2 | *AP3B1* | $\beta$3A of AP3 | Autoimmune/autoinflammatory diseases |
| X-linked lymphoproliferative disease | | | "Macrophage activation syndrome" |
| Type 1 | *SH2D1A* | SAP | (sJIA, SLE, Kawasaki disease, etc.) |
| Type 2 | *XIAP* | XIAP | |

Table 3: Classification of primary and secondary HLH [2]. Abbreviations: $\beta$3A of AP3, $\beta$3A subunit of adaptor protein 3; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HLH, hemophagocytic lymphohistiocytosis; LYST, lysosomal trafficking regulator; SAP, SLAM-associated protein; sJIA, systemic juvenile idiopathic arthritis; SLAM, signalling lymphocyte activation molecule; SLE, systemic lupus erythematosus; XIAP, X-linked inhibitor of apoptosis.

CRP, elevated ESR, elevated serum LDH levels. The clinical presentations and the above mentioned laboratory findings aided in suspecting HLH. Serum ferritin is a widely available and affordable biomarker for diagnosis of HLH especially in countries where facilities for genetic testing and specialised tests such as NK cell activity and soluble interleukin 2(sIL2) receptors are not available. Hyperferritinemia can be a result of inflammation, severe infection, chronic iron overload and uncommon pathology like HLH [23]. However, ferritin level of $>$ 10000 ng/mL appear to be specific and sensitive for HLH which should be correlated with the clinical and other laboratory findings [15, 7]. The child in our case had extremely elevated level of ferritin 20337 ng/mL with other laboratory findings indicative of HLH.

Diagnosis of HLH is based on molecular gene detection or presence of five out of eight HLH-2004 diagnostic criteria [4]. Our case fulfilled 6 of 8 2004-HLH diagnostic criteria as mentioned in table 2. A new tool, the "H score" has been developed to estimate the probability of HLH, which incorporates graded clinical and laboratory parameters, such as immunosuppression, fever, organomegaly, level of triglycerides, ferritin, alanine aminotransferase, fibrinogen, degree of cytopenia and the presence of hemophagocytosis on the bone marrow aspirate. An H-score of $>=$ 250 confers a 99% probability of HLH, where a score of $>=$90 confers a $>$1% probability of HLH [8].In our case, a total H-score of 289 assured $>$99% probability of HLH. Investigations for diagnostic evaluation of primary or secondary cause of HLH was sent. Simultaneously, treatment was initiated with dexamethasone administration as per HLH-94 protocol. Rapid improvement in clincal symptoms and laboratory findings were observed within 24 hours of initiation of dexamethasone. But no specific cause of primary and secondary HLH was identified as the panel of molecular genetic tests tested negative for *AP3B1, ITK, PRF1, SLC7A7, BLOC1S6, LYST, RAB27A, STX11, CD27, MAGT1, SH2D1A, STXBP2, UNC13D* gene excluding primary HLH. Tests for EBV, CMV, SARS-CoV-2, Scrub typhus, malaria, dengue, chikungunya, leptospirosis, brucellosis showed negative results for secondary trigger of HLH. Even if, no obvious causative agent triggering HLH was isolated, child was successfully treated as per HLH-94 protocol guidelines with dexamethasone.

# 4 Treatment

Initial treatment for the child was started with broad spectrum antibiotics intravenous meropenem and vancomycin suspecting sepsis but there was no clinical improvement. Subsequently, after the arrival of laboratory findings, child was suspected to have HLH and intravenous dexamethasone was started at 10mg/m$^2$/day as per HLH-94 treat-

ment protocol. The child was clinical stable and laboratory findings improved within 24 hours of dexamethasone administration. With the gradual clinical stability, and improvement in laboratory parameters child was discharged after 10 days of hospital stay on oral dexamethasone at 10 mg/m$^2$/day, oral lansoprazole (lanzol JR) 7.5mg/day and syrup vitamin D3 (400 IU/mL) 1mL/day till one year of age. Parents were counselled regarding the rarity of the disease, possibilities and prognosis of primary and secondary HLH. They were advised to continue the child on oral dexamethasone on a tapering dose for 8 weeks (10 mg/m$^2$ for 2 weeks, 5 mg/m$^2$ for 2 weeks, 2.5 mg/m$^2$ for 2 weeks, 1.25 mg/m$^2$ for 1 week, and taper and discontinue during 1 week, then pulses every second week with 10mg/m$^2$ for 3 days) with continuous monitoring of laboratory parameters. They were made aware about the possibility to add chemotherapeutic medications or adopt HSCT (hematopoietic stem cell transplantation) as the definitive management of HLH as per HLH-94 treatment guidelines, if primary HLH arrives or if any deterioration occurs (clinical/laboratory findings) in between and counselled regarding the importance of follow up.

# 5 Outcome and follow up

The child was well managed with 8 weeks of dexamethasone as per HLH 94 protocol with no reappearance of symptoms in between. A follow up visit was made with the negative investigation reports for genetic workup and serological tests for various infectious agents that helped in excluding primary and secondary cause of HLH and the child was clinically stable.

# 6 Conclusion

HLH being a fatal syndrome, it could be treatable with corticosteroids, if timely intervention is made, like in the above-mentioned case. Hence, it is recommended that therapy should be started in cases with high suspicion after the diagnostic evaluation is initiated without waiting for all results to be obtained. The correlation of serum ferritin level with clinical presentations can help in obtaining good clinical outcomes and prevent mortality in a resource-limited setting.

# 7 Acknowledgement

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# 8 Authors contribution

Santoshi Pokharel contributed to conceptualizing, data collection, and writing the manuscript. Shankar Pokharel and Geeta Bashyal contributed to the writing and reviewing.

# 9 Consent

This case was written and published with the consent of the legal parents of the patient.

# 10 Data Availability

The data used to support the findings of this study are included in the article.

# 11 Conflict of interest

None declared.

# 12 Financial support and sponsorship

None.

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