Idiopathic Hemophagocytic lymphohistiocytosis (HLH) in an 8-Month-Old male child : A Case Report

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Abstract

Hemophagocytic lymphohistiocytosis (HLH) has varied clinical presentations. A prompt recognition and initiation of appropriate treatment can prevent cytokine storm and fatal outcome. We report an 8-month-old male child presented with non-specific clinical complaints and hyperferritinemia, diagnosed as idiopathic HLH and successfully treated with dexamethasone.

Key clinical message: Hemophagocytic lymphohistiocytosis (HLH) might present with wide array of clinical presentations. A prompt recognition and initiation of appropriate treatment can prevent cytokine storm and fatal outcome.

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, prevalence of HLH was calculated 1 in 100,000 [2, 13]. HLH can present as the primary syndrome or occur secondary to variety of conditions such as infections, malignancies, autoimmune and autoinflammatory disorders [2, 16]. Early recognition and initiation of specific management of HLH is often challenging as both the subtypes share the 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 increased risk for both receipt of critical care and subsequent death [21]. We hereby discuss a case of 8-month-old male child presented with persistent high fever, erythematous body rash, generalized body swelling and oliguria, bicytopenia, hypertriglyceridemia, hypofibrinogenemia and highly elevated ferritin level of > 20000ng/mL, successfully managed with eight weeks of dexamethasone administration.

2 Case description

An 8-month-old male child was brought with the presenting complaint of fever for 20 days, generalized body rash for 16 days, generalized body swelling and decreased urine output for 7 days, with multiple visits in other hospitals. After having excessive irritability for about a week, child developed acute onset of fever with maximum documented temperature 104 degree Fahrenheit, not associated with chills and rigor, no diurnal variation, relieved on antipyretics. After 4 days of fever, he developed eye redness with no eye discharge followed by development of rash on face which progressively increased to involve whole body. He was treated with oral azithromycin and cefpodoxime which didn't relieve his symptoms. He was admitted in a tertiary level hospital where he received intravenous piperacillin/tazobactam (ZOSYN), amikacin, doxycycline, and intravenous hydrocortisone for 2 days. He got discharged after 2 days as his symptoms started decreasing. He continued to develop intermittent fever and started passing greenish-yellow semisolid stool almost 5-6 times a day, non-mucoid, non-blood stained, not associated with pain abdomen. He then developed generalized body swelling starting from abdomen, along with

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decreased urine output for which he was admitted in a private hospital for 10 days. The laboratory findings during the period of hospital stay are summarized in table 1.

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 μL)	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 98 degree Fahrenheit, heart rate 148 bpm, respiratory rate 47/min and oxygen saturation 95% at room air. His length and weight were recorded as 68 cm and 8.4 kg,implying the normal weight-for-length(≥ -2 to ≤ 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. Abdomen was mildly distended, umbilicus was central and slit shaped, 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, other investigations were sent to rule out various causes including HLH, as he had very high ferritin level and deranged liver enzymes. Hemogram revealed bicytopenia (hemoglobin 7.7gm/dL, platelets 85000/mm^3), elevated total leukocyte count 16,600/mm^3, differential leukocyte count showed 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 abdomen revealed mild ascites, enlarged liver measuring 10.6 cm size with normal echotexture, enlarged spleen measuring 8.4 cm size. 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), 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 upper dermis. However, eosinophils/ vasculitis were not identified in the section examined. 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 showed normocellular marrow with hematopoietic elements of all three series with no atypical cells. Other investigations revealed, 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 μg/dL(reference range: 75-291 μg/dL), 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. Finally, by excluding other causes, as well as according to the clinical findings and laboratory data that met the 2004-HLH diagnostic criteria [4] (see table 2), the diagnosis of idiopathic HLH was done.

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	$< 100000/mm^3$	$85000/mm^3$
• 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	≥ 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 exclude the primary cause of HLH, a panel of molecular genetic tests were performed and the child was started on intravenous dexamethasone at $10mg/m^2$ per day following HLH-94 treatment protocol [1]. The child attained clinical stability within 24 hours and improvement in laboratory findings was observed as shown in figure 1.

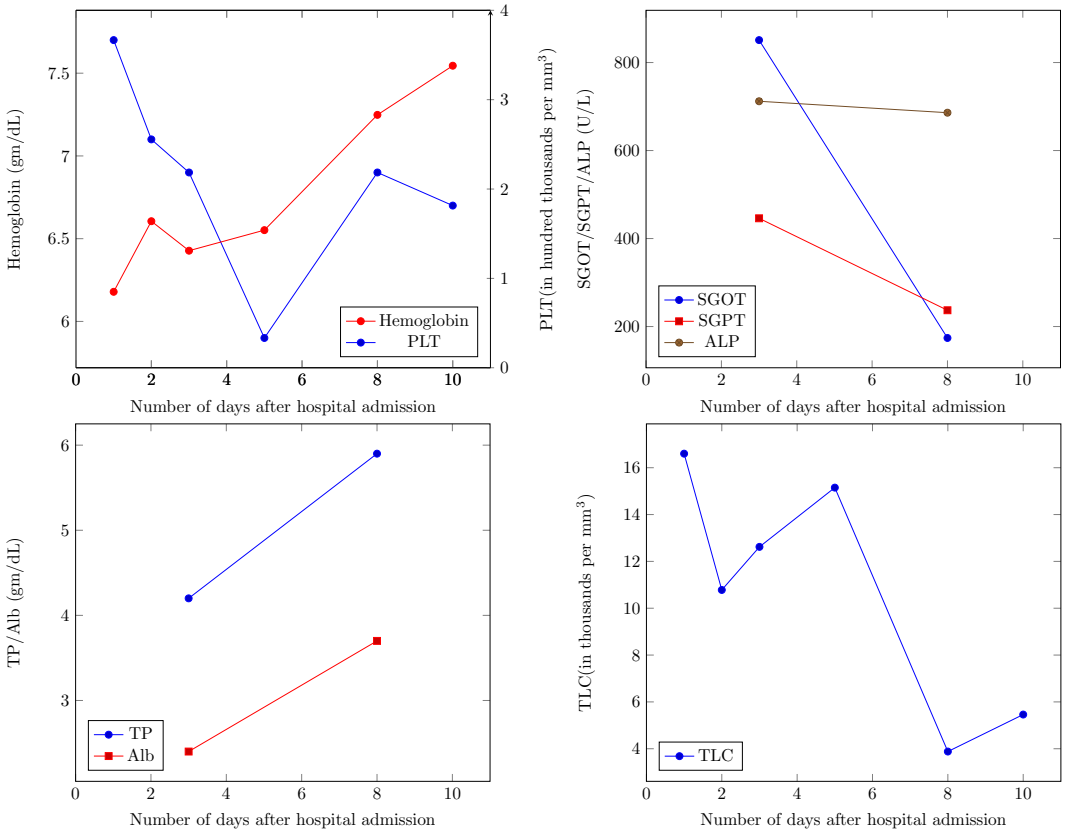

Figure 1: Graphs showing the trend of Hb, PLT, SGOT, SGPT, ALP, TP, Alb and TLC over a period of a few days after the administration of dexamethasone.

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-α), interleukin (IL-6 and IL-12), interferon gamma (IFNγ) 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] and inflammatory conditions making the definitive diagnosis and management often challenging. HLH has varied clinical and laboratory presentations like persistent high grade fever, hepatosplenomegaly, petechial or purpuric rash, diarrhoea, abdominal pain, progressive cytopenia, hypertriglyceridemia, hypofibrinogenemia, hyperferritinemia, elevated transaminases levels and elevated serum LDH levels, often involving multiple organ-systems.

In our case, child presented with high grade fever of 104 degree Fahrenheit, erythematous macular rash, generalized anasarca, oliguria. It was suspected to be infectious in origin and initially treated with antibiotics. However, culture of blood and urine did not reveal any microbial growth. As the child was symptomatic since 20 days, differential diagnosis of Atypical Kawasaki disease was thought of but it was ruled out as there was no change

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*	β3A 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: β3A of AP3, β3A 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.

in lips and oral cavity, absence of cervical lymphadenopathy and no periungual desquamation. ECHO suggested absence of coronary artery dilatation or aneurysms. Also, normal value of ANA, p-ANCA, c-ANCA, C3 and C4 ruled out the possibility of autoimmune and autoinflammatory disorders. Tests for EBV, CMV, Scrub typhus, malaria, dengue, chikungunya, leptospirosis resulted negative results. Furthermore,laboratory findings were suggestive of anemia, thrombocytopenia, hypofibrinogenemia, hypertriglyceridemia, hyperferritinemia, highly elevated liver enzymes, elevated CRP, elevated ESR, elevated serum LDH levels. 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]. 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 which aided in diagnosis 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 scoring system, the "H score" has been developed to estimate the probability of HLH, which incorporates graded clinical and laboratory parameters, such as immunosuppression, fever, organomegaly, levels 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, the H score revealed a total score of 289 with $>$99% probability of HLH. To identify the specific cause of HLH, the panel of molecular genetic tests were undertaken which tested negative for *AP3B1, ITK, PRF1, SLC7A7, BLOC1S6, LYST, RAB27A, STX11, CD27, MAGT1, SH2D1A, STXBP2, UNC13D* gene excluding primary HLH. No obvious causative agent triggering secondary HLH was isolated and the patient condition was described as idiopathic HLH.

4 Treatment

Initially, treatment was started with broad spectrum antibiotics intravenous meropenem and vancomycin suspecting infection but there was no clinical improvement. Subsequently, with the appearance of laboratory findings, child was started on intravenous dexamethasone at 10mg/m^2/day as per HLH-94 treatment protocol. Clinical stability and

laboratory findings of child 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 admission on oral dexamethasone at 10 mg/m^2/day, oral lanzol JR 7.5mg/day and syrup vitamin D3 (400 IU/mL) 1mL/day till one year of age. Parents were counselled regarding the disease, possibilities and prognosis of primary and secondary HLH. As the child was improving on dexamethasone, they were advised to continue child on oral dexamethasone on 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) and were made aware to add medications as per HLH-94 treatment protocol if primary HLH arrives or if any deterioration occurs (clinical/laboratory findings) in between.

5 Outcome and follow up

The child was well managed with 8 weeks of dexamethasone in tapering dose with no remission in between. A follow up visit was made with the tests result excluding primary and secondary HLH. Subsequent visits were not made.

6 Conclusion

HLH being a fatal syndrome, it is potentially a treatable condition. Diagnosis of HLH is often missed because of lack of suspicion, wide variety of non-specific presentations, inability to fulfill all the diagnostic criteria and lack of availability of diagnostic tests in a resource limited settings. Our study suggests, an estimation of serum ferritin level could be used as an important investigation tool for diagnosis of HLH as it is a widely available and affordable biomarker even in a resource limited setting. Prompt recognition and initiation of treatment helps in preventing morbidity and mortality from HLH.

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8 Authors contribution

Santoshi Pokharel contributed in conceptualizing, data collection and writing the manuscript. Shankar Pokharel contributed in 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 within the article.

11 Conflict of interest

None declared.

12 Financial support and sponsorship

None.

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