



# Hemophagocytic lymphohistiocytosis in an infant with multiple triggers!!

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## Abstract:

Hemophagocytic lymphohistiocytosis (HLH) is a disorder of immune dysregulation secondary to a massive unregulated cytokine storm and its downstream consequences. HLH is being increasingly recognized as a cause of pyrexia of unknown origin, unexplained cytopenias, and hepatic dysfunction. However, this potentially treatable condition is often missed due to lack of suspicion, variable, and nonspecific presentations, inability to fulfil all the diagnostic criteria and availability of diagnostic tests in resource limited settings. Both familial and acquired forms of HLH can be triggered by multiple factors in a susceptible patient. We report a 9-month old infant who developed HLH in association with Stevens–Johnson syndrome following massive blood transfusion.

## Keywords:

Graft versus host disease, massive blood transfusion, organomegaly, pancytopenia, rash

## Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a disorder of immune dysregulation secondary to a massive unregulated cytokine storm and its downstream consequences. It may pose as a diagnostic challenge to the clinician due to its non specific presentations as pyrexia of unknown origin, unexplained cytopenias and hepatitis. A high index of suspicion is required to clinch the diagnosis based on clinical features and limited availability of diagnostic test in resource limited settings. We report a 9-month old infant who developed HLH in association with Stevens–Johnson syndrome following massive blood transfusion.

## Case Report

A 9-month-old boy, 2<sup>nd</sup> progeny of a nonconsanguineous marriage presented with generalized skin rash and fever for 1 week. Three days before the onset of symptoms, he had running nose and loose stools which settled spontaneously over the next 2 days. Routine blood investigations done before

presentation revealed anemia (haemoglobin 6.8 g/dl) with borderline normal total leukocyte count (4000/cu mm). Other blood counts were not available. He received antibiotics (intravenous injection ceftriaxone and injection amikacin and also oral amoxicillin) and packed red blood cells (approximately 40 ml/kg of body weight). The indication for blood transfusion was not clear, and child was transfused with group matched whole blood (one unit) donated by his uncle. High-grade fever and rash developed 3 days following the packed cell transfusion. The rash was initially noticed on the trunk which spread over face and limbs, eyes, and involved mucosa of oral cavity. There was no history of abortions or sibling deaths in the family.

Examination revealed a sick looking child, with generalized plethoric skin with papules and vesicles filled with clear fluid along with peeling of the skin involving entire body and oral mucosa. Conjunctival membrane was involved with eyelid edema and mucopurulent discharge. He was febrile

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**Table 1: Investigations of the index case at presentation (post massive transfusion)**

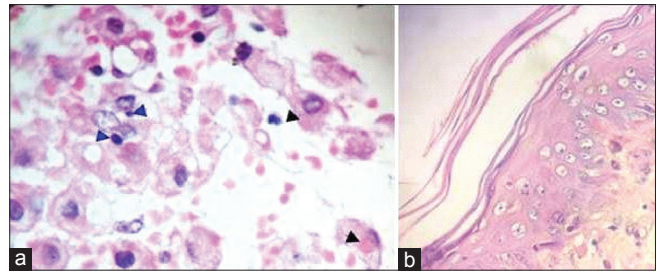
Investigation	Result	Reference range
HB	16.1 g/dl	10.0-13.2 g/dl
Total leukocyte count	1400/ $\mu$ L	6-17.2 $\times$ 103/ $\mu$ L
Differential count	N 24, L 70	N - 15-45, L - 47-77
Platelet	40,000/cu mm	1.5-4.5
Alanine transaminase	112 IU	13-45 IU/L
Aspartate transaminase	27 IU	9-80 IU/L
Total bilirubin	3.12 mg/dl	<1.2 mg/dl
Direct bilirubin	2.09 mg/dl	<0.2 mg/dl
Serum albumin	2.79 g/dl	2.2-4.8 g/dl
Prothrombin time	17.1 s	11.5-15.3
INR	1.41	0.86-1.22
CRP	9.9 mg/L	0-5 mg/L
USG abdomen	Hepatosplenomegaly	

HB = Hemoglobin, AST = Alanine transaminase, CRP = C-reactive protein, INR = International normalized ratio, USG = Ultrasonography, N = Neutrophil, L = Lymphocyte

and irritable but hemodynamically stable. Abdominal examination was remarkable for hepatosplenomegaly while examination of other systems was within normal limits. Investigations of the child at presentation to our center are summarized in Table 1.

He was started on broad spectrum antibiotics. Work up done for infectious etiology including blood culture, urine culture, malarial antigen test, serology for dengue, chikungunya, leptospirosis, and rickettsia was negative. Cytomegalovirus (CMV) polymerase chain reaction in urine was positive with 12000 copies/ml which may explain the pretransfusion anemia and low normal total counts. However, possibility of transfusion associated CMV transmission cannot be ruled out. Screening for autoimmunity (Direct Coomb's test and antinuclear antibody) was noncontributory. Incidentally, serum vitamin B 12 was found to be 91 pg/mL (normal range 200–835 pg/mL), probably contributing to pancytopenia. General condition of the child deteriorated further by day 3 of hospitalization, with persistent fever and bleeding per rectum. Blood counts further decreased on day 3 with total leukocyte count 700/cu mm, and platelet count of 25,000/cu mm; however, haemoglobin remained at 16.2 g%. S. Ferritin was 2529 ng/ml. In view of fever, pancytopenia, organomegaly, raised serum ferritin a possibility of hemophagocytic syndrome was considered, and a bone marrow aspirate was performed but it was inconclusive.

On day 4, C-reactive protein was increased to 185 mg/L. However, erythrocyte sedimentation rate (ESR) was only 5 mm/h, probably reflecting hypofibrinogenemia in the present clinical context. He was treated with granulocyte colony-stimulating factor and steroids as per hemophagocytic lymphohistiocytosis (HLH)



**Figure 1:** Hemophagocytic lymphohistiocytosis (a, H and E,  $\times$ 400). Bone marrow biopsy showing hypocellular marrow showing presence of histiocytes with engulfed lymphocytes (blue arrow head on left side) and red blood cells (black arrow head on right side). Skin biopsy showing parakeratosis, acanthosis, and necrotic keratinocytes (b, H, and E,  $\times$ 400)

protocol. Total counts decreased to 370/cu mm at day 5 with worsening of liver functions. He succumbed to death on day 8 of hospitalization due to refractory shock. Postmortem bone marrow biopsy [Figure 1a] showed extensive hemophagocytosis; skin biopsy [Figure 1b] showed acanthosis; and presence of necrotic keratinocytes in the epidermis suggestive of toxic epidermal necrolysis (TEN) and liver biopsy revealed micro and macro steatosis. Multiple triggers, namely, CMV infection, massive blood transfusion, and Stevens–Johnson syndrome (SJS), all of which may predispose to hemophagocytic syndrome were identified in the patient.

## Discussion

Our index case had persistent high-grade fever, hepatosplenomegaly, and pancytopenia, but all the evaluation done for infection was negative; hence, a differential of HLH versus transfusion-associated graft-versus-host disease (TA-GVHD) was kept. Table 2 shows the differentiating feature of these two.<sup>[1-6]</sup> There was an absence of gastrointestinal symptoms commonly seen in TA-GVHD. A low ESR also pointed towards the possibility of HLH with macrophage activation syndrome. Bone marrow biopsy showed predominantly hemophagocytosis in our case whereas bone marrow is characteristically aplastic in TA-GVHD. Characteristic histopathological changes in skin and liver in TA-GVHD were not seen in the present case.

Hemophagocytic lymphohistiocytosis (HLH) is an under recognized cause of unexplained fever, cytopenias mimicking sepsis, and multiorgan dysfunction. Delay in diagnosis and treatment leads to high mortality in this condition.<sup>[7]</sup> As per a recent review, tertiary care pediatric centers should expect 1 case of HLH per 3000 inpatient admissions.<sup>[8]</sup> We report a case of HLH with multiple triggers, including CMV infection, SJS, and blood transfusion. So far, only eight cases have described the association of TEN and HLH.<sup>[9,10]</sup>

**Table 2: Comparison of hemophagocytic lymphohistiocytosis and transfusion associated graft versus host disease (TA-GVHD)**

	HLH	TA-GVHD
Pathogenesis	Deficiency of perforin mediated cytotoxicity leading to uncontrolled macrophage activation, cytokine storm and its effects	Viable donor lymphocytes attack the host cells in immunocompromised or partial HLA matching of recipient with the donor in immunocompetent host
Clinical features		
Organs involved	Skin, liver, bone marrow, central nervous system, and lymph nodes	Skin, liver, gastrointestinal tract, bone marrow
Predisposing factors	Rheumatological condition, malignancy, immunodeficiency, infections	Immunocompromised, hematopoietic stem cell transplant recipient, partial HLA matching with donor
Clinical presentation	Febrile illness with multiorgan involvement	2 days to 6 weeks after cessation of transfusion with characteristic rash and other organ involvement
Diagnosis	Genetic testing for mutation or HLH 2004 diagnostic criteria	Clinical syndrome with characteristic histopathology, circulating lymphocytes showing different phenotype than host cells
Histopathology		
Bone marrow	Hemophagocytosis	Aplasia
Liver	Sinusoidal dilatation with hemophagocytic histiocytosis	Eosinophilic infiltration, small bile duct degeneration, peripheral inflammation, lymphocyte infiltration
Skin	Nonspecific	Vacuolization of the basal layer and histiocytic infiltrate, and sometimes the pathognomonic finding of satellite dyskeratosis

TA-GVHD = Transfusion-associated graft-versus-host disease, HLH = Hemophagocytic lymphohistiocytosis, HLA = Human leukocyte antigen

HLH syndrome is characterized by excessive inflammation due to uncontrolled macrophage cell activation and failure of normal negative feedback from cytotoxic T cells and natural killer (NK) cells. Multiple triggers such as viral, bacterial, protozoal, and rickettsial infections or those leading to immunodeficiency such as malignancy, rheumatological disorders, or HIV infection leading to immune activation have been identified in both primary and secondary forms of disease. It is not uncommon to find multiple triggers in the same patient as in our case.<sup>[11]</sup> Both TEN and HLH are characterized by defective activation of cytotoxic CD8+ lymphocytes and elevation of serum granulysin, which is a likely explanation of the association of the two conditions.<sup>[10]</sup> Pancytopenia in SJS can be early marker of associated HLH as in our case.<sup>[12]</sup>

Diagnosis of HLH can be challenging due to limited specificity and sensitivity of these criteria mimicking common infections, malignancy, and autoimmune disorders. Diagnosis of HLH is made based on standard criteria described in HLH 2004 guidelines.<sup>[13]</sup> Genetic testing and soluble CD25 receptor are specific tests but usefulness is limited in resource-limited settings.<sup>[14]</sup> Demonstration of hemophagocytosis on bone marrow aspirate is a relatively less sensitive and specific criteria, requires an invasive procedure and its absence does not exclude HLH.<sup>[8]</sup> However, elevated ferritin can be useful marker in diagnosis with good sensitivity (90%) and specificity (96%), especially when >10,000 ng/ml.<sup>[15]</sup> All these criteria may not be present at one point of time and evolve over a period in the course of disease and the same was reflected in our case as the repeat bone marrow examination revealed evidence of HLH with the initial one being noncontributory.<sup>[13]</sup> Moreover,

these diagnostic criteria do not represent all the clinical findings of HLH. A modification of these criteria proposed by Filipovich, includes hepatitis along with fever, splenomegaly, cytopenias, and four immune markers including hemophagocytosis, increased ferritin, hypofibrinogenemia, absent or decreased NK cell function.<sup>[1]</sup> As seen in the index case, hepatic inflammation is commonly associated with HLH and diagnosis is unlikely in absence of hepatic involvement.<sup>[8]</sup>

Differential diagnosis can be varied ranging from infection and sepsis to drug reactions, liver disease, autoimmune lymphoproliferative syndrome, HLH associated with underlying rheumatological condition. The index child also had a history of blood transfusion from a related donor; hence, TA-GVHD was also considered as a possibility. TA-GVHD can occur after 2 days to 6 weeks of transfusion in immunocompetent hosts who have a partial human leukocyte antigen match with donor.<sup>[2]</sup> It presents with a similar clinical findings; even elevated ferritin and hemophagocytosis in bone marrow may be present. However, as per the National Health and Safety Network criteria, specific skin or liver biopsy finding are required for definitive diagnosis.<sup>[2]</sup>

In cases of HLH, early treatment is essential for positive outcome; hence, it is recommended that therapy should be started in cases with high suspicion after diagnostic evaluation is initiated without waiting for all results to be obtained.<sup>[2]</sup> Initial therapy can include corticosteroids, with or without cyclosporine A along with robust control of underlying infectious or rheumatological disease.

Lack of genetic testing for HLH and CMV virus culture to know the CMV disease status of the patient were the limitations of this case. The practice of blood transfusion given from related donors is a concern highlighted in this case as it is still widely practiced in remote areas with limited resources.

## Conclusion

Early and high index of suspicion is essential to avoid missing the window of treatment for a favorable outcome in HLH. HLH should be included in the differential diagnosis of prolonged fever, refractory cytopenia, and hepatitis. All diagnostic criteria may not be present at a single point emphasizing the importance of serial monitoring of the diagnostic parameters in critically ill children. A note should be made that blood transfusions in anemia of undiagnosed etiology should be avoided unless it is a life-threatening emergency.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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## Conflicts of interest

There are no conflicts of interest.

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