CASE REPORT

Familial hemophagocytic lymphohistiocytosis in an infant: A case report

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Abstract

Familial Hemophagocytic Lymphohistiocytosis (FHL) is a rare disorder of early childhood more prevalent in consanguineous families. We discuss a case of a 6-month-old female infant presenting with persistent fever, failure to thrive and neurological manifestations. Diagnosis of FHL type 2 was made based on clinical and laboratory parameters and confirmed with genetic testing. Child was started on intravenous corticosteroids under antibiotic coverage along with anti-epileptics and supportive care however the overall clinical condition did not improve and after 6 days of hospital stay the parents requested discharge and was lost to follow- up.

Keywords: Infant, Failure to thrive, Familial Hemophagocytic Lymphohistiocytosis

Introduction:

Hemophagocytic Lymphohistiocytosis (HLH), originally termed histiocytic medullary reticulosis, was first reported in 1939 when Scott and Robb-Smith documented a case of a child afflicted with a neoplastic histiocytic disorder [1]. The familial nature of this disorder was first recognised by Farquhar and Claireaux in 1952 [2]. HLH encompasses a group of syndromes characterized by multi-organ infiltration and hematological suppression, stemming from the excessive release of inflammatory cytokines. HLH represents an immune disorder driven by the uncontrolled activation of T lymphocytes and macrophages. Clinically, it manifests with persistent fever, pancytopenia, and hepatosplenomegaly, alongside the characteristic finding of hemophagocytosis in the bone marrow, liver, spleen, and lymphatic tissue. Primary HLH comprises Familial Hemophagocytic Lymphohistiocytosis (FHL) and primary immunodeficiency syndrome, with FHL often linked to consanguinity or known genetic mutations. Mutations in genes such as PRF1, UNC13D, STX11, and STXBP2, impair cytotoxic and Natural Killer (NK) cells' function, resulting in uncontrolled immune activation. Particularly, PRF1 mutation impairs perforin expression leading to unchecked cytokine production and macrophage activation. These genetic insights highlight heterogeneous nature and pathophysiology of FHL [3-5]. We report an interesting case of an infant with FHL type 2.

Case Report

A 6-month-old female infant born to third-degree consanguineous parents by normal vaginal delivery, with a birth weight of 2.3 kg. She was discharged without neonatal intensive care unit admission, at 3 days of age. At 4 months of age, the child experienced fever accompanied by generalized tonic-clonic seizures, diagnosed as meningitis, and partially treated at another centre. The family history included prior pregnancy that was

medically terminated after 20 weeks due to suspected cardiac anomaly, raising concern for an inherited or syndromic condition. On presentation, the child had been suffering from recurrent moderate-grade fever for the past 3 months, responsive to anti-pyretics, without diurnal variation or respiratory symptoms. She experienced frequent projectile vomiting post-feeding, alongside upper abdominal distension and pain, though stools remained regular. Notably, there were no signs of jaundice or bleeding tendencies. Developmentally, the child had regressed, unable to hold her head as previously achieved, with intermittent grasping and diminished social interaction. Vision and hearing impairments had also been noted, alongside stunted growth. An episode of abnormal movements, characterized by uprolling of eyes, occurred two months prior. There was no history of ear discharge, feeding difficulties, constipation, or abnormal urinary symptoms.

Immunization records show completion of birth doses and subsequent vaccinations. Physical examination revealed deviations from expected values in length, weight and head circumference [{length 61 cm (< third centile), expected being 67 cm}, {weight 5.5 kg. (< third centile), expected being 7.7 kg}, and {head circumference was 38.5 cm- less than 3 standard deviation (microcephaly), expected being 43 cm}]. Vital signs showed fever (101^0F) and tachycardia (154/ min). Clinical findings included bulging anterior fontanel, flat nasal bridge, low set ears, and a malformed right ear. Abdominal examination revealed tense distension, significantly palpable liver and spleen, with bowel sounds present. Cardiorespiratory examination was within normal limits. Neurological examination revealed irritability, hypotonia in all limbs, and bilateral flexor plantar reflexes. Laboratory examination revealed significant findings as mentioned in Table 1.

Table 1: Laboratory findings in present case

Parameters	Values	Normal reference range
Bicytopenia **Hemoglobin** **Platelet count**	 7.1 g/dL 102.0 x 10^3/µL	 11.1-14.2 g/dL 150-400 x10^3/µL
Elevated LDH	518 U/L	160-370 U/L
Hyperferritinemia	588.0 ng/mL	13.0-150 ng/mL
Hypertriglyceridemia	450 mg/dL	60-150 mg/dL
Hypoalbuminemia	2.30 g/dL	3.8-5.4 g/dL
Hyponatremia	121.0 mmol/L	Premature: 128 - 148 mmol/L Newborn:133 - 146 mmol/L Child: 138 - 145 mmol/L
Lumbar puncture: **Elevated white blood cell count** **Elevated protein** **Low glucose**	80 cells, with predominantly lymphocytic pleocytosis >200 mg/dL 22 mg/dL	 0-30 cells 15-45 mg/dL 60-80 mg/dL
TORCH complex testing	Negative	Negative

Abdominal ultrasound revealed hepatosplenomegaly with normal echotexture. MRI brain exhibited bilateral cerebellar abnormalities suggestive of acute cerebellitis and features consistent with meningitis. Additionally, there were confluent T2/FLAIR hyperintensities involving deep and periventricular white matter, likely sequelae of previous insult. EEG showed abnormal epileptiform discharges. Bone marrow aspiration revealed normocellular marrow with marked erythroid dyspoiesis and few scattered macrophages seen, occasional showing hemophagocytosis (Figures 1 and 2). In view of the clinical and biochemical parameters, FHL was suspected. Whole exome sequencing confirmed the diagnosis of Familial HLH 2, revealing a homozygous missense variant (c.1489T > C, (p. Cys497Arg)), {Amino acid conserved by GERP++ PhyloP}.

The child received intravenous broad-spectrum antibiotics to address potential infectious triggers. Intravenous dexamethasone was started under the cover of antibiotics. Additionally, she required two anti-epileptic drugs to control the seizures. Adequate electrolyte corrections and intravenous fluids (colloids, crystalloids) were also given.

Furthermore, owing to the observed anemia, two units of packed red blood cells were transfused to optimize the child's hemoglobin levels and tissue oxygenation. Overall clinical condition did not improve during the hospital stay. The child's parents decided to discontinue treatment and took discharge after 6 days of hospital stay and was lost to follow-up.

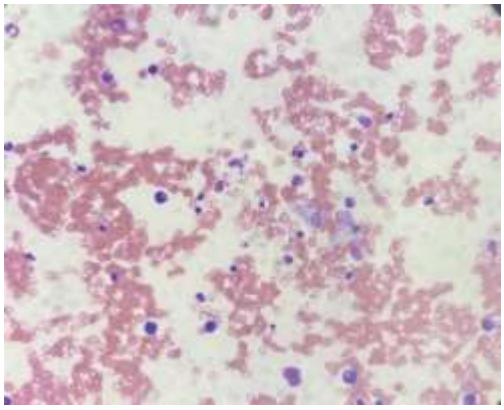

Figure 1: Bone marrow aspirate showing hemophagocytosis of platelets and neutrophils

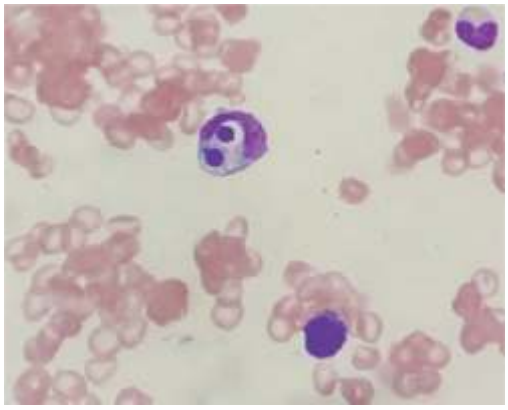

Figure 2: Bone marrow aspirate showing hemophagocytosis of erythroid precursor cell

Discussion

FHL is a disorder of early childhood. The condition was shown to be more prevalent in consanguineous families, suggesting an autosomal recessive pattern of inheritance. The incidence of FHL is 0·12/ 100,000 children born per year, with a male to female ratio of 1:1 [2]. Typically, FHL presents early in life, with approximately 70-80% of cases manifesting within the first year, with the peak age of presentation between 1 and 6 months of age [2, 6]. FHL typically manifests with fever, hepatosplenomegaly, and cytopenias as its hallmark symptoms. Fever is often persistent, and hepatosplenomegaly tends to worsen progressively. Lymphadenopathy is present in less than 50% of the cases. Skin manifestations such as transient maculopapular, nodular, or purpuric rashes are frequent, affecting about 30-40% of cases, often accompanied by high fever. Neurological abnormalities are prominent, especially in advanced stages, with symptoms ranging from irritability, neck stiffness, and seizures in younger patients, to cranial nerve palsies, hemiplegia/tetraplegia, and signs of raised intracranial pressure. Infections, particularly viral infections like Epstein–Barr Virus (EBV), cytomegalovirus, and parvovirus, commonly trigger FHL [2-8]. Our patient was a 6-month-old female child born to a consanguineous marriage with low birth weight presenting with recurrent fever (pyrexia of unknown origin) with neurological signs and symptoms (seizures, hypotonia, irritability) for 3 months and failure to thrive. Hepatosplenomegaly was also seen in the child.

In HLH, the diagnostic criteria have evolved to provide a comprehensive framework for accurate diagnosis. Initially defined in 1991, the diagnostic criteria emphasize clinical, laboratory, and histopathological features. Clinically, fever and splenomegaly are cardinal signs. Laboratory criteria include cytopenia in at least two lineages (hemoglobin < 90 g/l, platelets < 100 × 10^9/l, neutrophils < 1.0 × 10^9/l), hypertriglyceridemia (> 2.0 mmol/l or > 3 SD, fasting values), and/or hypofibrinogenemia (< 1.5 g/l or < 3 SD). Histopathological confirmation requires presence of hemophagocytosis in bone marrow or other reticuloendothelial tissues in the absence of malignancy. The HLH-2004 protocol introduced modifications, requiring fulfilment of five out of eight diagnostic criteria for diagnosis. These include the initial criteria plus additional parameters as listed in Table 2.

Table 2: Revised diagnostic criteria for Hemophagocytic lymphohistiocytosis (HLH) 2004

Initial diagnostic criteria	**Additional criteria**
1. Fever 2. Splenomegaly 3. Cytopenia affecting at least two of the three lineages in the peripheral blood Haemoglobin < 90 g/l (in neonates < 10 g/l), platelets < 100 × 10^9/l, neutrophils < 1.0 × 10^9/l). 4. Hypertriglyceridaemia (> 3.0 mmol/l fasting value) and/or hypofibrinogenemia (< 1.5 g/l), 5. Hemophagocytosis in bone marrow, spleen or lymph nodes No sign of malignancy	6. Low/absent natural killer cell activity 7. Hyperferritinaemia (> 500 ug/l) 8. High soluble interleukin 2 receptor levels (> 2400 U/ml).

Molecular findings such as mutations in the perforin gene or hMunc 13-4 gene can also confirm primary (familial) HLH. Additional investigations recommended for comprehensive evaluation include serum transaminases (often elevated) and examination of spinal fluid, with caution to exclude increased intracranial pressure before lumbar puncture. These criteria and recommendations ensure a thorough diagnostic approach to HLH, reflecting advancements in understanding and diagnosing this complex condition [9-10]. In our patient the diagnosis was considered as patient met clinical and laboratory criteria (fever, elevated LDH, high serum ferritin, hypertriglyceridemia, hemophagocytosis in bone marrow) meeting 6 of 8 criteria. The diagnosis of FHL type 2 was further confirmed by genetic testing (whole exome sequencing) showing a homozygous missense variant (c.1489T > C, (p. Cys497Arg)), {Amino acid conserved by GERP++ PhyloP}.

If left untreated, FHLis rapidly fatal, typically resulting in death within a median of 2 months. Patients succumb to severe infections or systemic inflammation leading to multi-organ failure. Treatment focuses on managing infectious triggers and immune dysregulation initially with chemotherapy, followed by definitive therapy such as hematopoietic stem cell transplant (HSCT). Early intervention is critical to improve survival outcomes [2, 8]. In our patient corticosteroids, antibiotics and supportive care were initiated. However overall clinical condition did not improve during the hospital stay. Addition of chemotherapeutic agents and HSCT was considered, however the parents requested for discharge in this case and child was lost to follow-up.

Our findings are in alignment with the case described by Almalky *et al*., who reported a similar case of a 2-year-old boy from a consanguineous family, with no prior history of genetic diseases. The child met five HLH-2004 criteria with persistent fever, hepatosplenomegaly and bicytopenia, elevated liver enzymes, hyperferritinemia and hypofibrinogenemia. Despite the absence of hemophagocytosis in the bone marrow and limited access to NK cell function testing, the diagnosis was strengthened by the identification of a novel homozygous frameshift mutation in the *PRF1* gene (p.F178fs), further supporting the diagnosis of FHL. Their patient responded favourably to immunochemotherapy (etoposide, dexamethasone, and cyclosporine A) and was placed on the waiting list for HSCT [5].

In contrast, Alasmari *et al*. reported a more severe case in a 37-day-old neonate born to consanguineous marriage with a significant family history of early sibling death. This patient also fulfilled six HLH-2004 criteria which includes fever, hepatosplenomegaly, cytopenia, elevated liver enzymes, hyperferritinemia and bone marrow hemophagocytosis. The patient was also found to have perforin deficiency on flow cytometry, with a subsequent whole exome sequencing confirming a homozygous PRF1 mutation. Despite early initiation of treatment, the infant's condition deteriorated rapidly and succumbed to multi-organ failure [8].

These cases reflect the aggressive nature of early-onset FHL, the diagnostic and therapeutic limitations and the diagnostic utility of genetic testing. Similar challenges were faced in our case.

Conclusion

FHL, particularly familial HLH 2 due to *PRF1* mutations, is a life-threatening condition requiring prompt diagnosis and treatment. Early initiation of treatment, including chemotherapy and HSCT, is crucial for improving survival outcomes. This case highlights the importance of genetic testing and adherence to diagnostic criteria in managing this complex disorder.

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