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Hemophagocytic lymphohistiocytosis in children- A case series

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Abstract

Hemophagocytic Lymphohistiocytosis (HLH) is a rare disorder in children characterised by immune dysregulation and is a potentially life threatening condition. Early initiation of therapy is found to reduce mortality in HLH. A high index of suspicion in children presenting with prolonged fever is needed for early diagnosis of HLH.

Abbreviations:

HLH: Hemophagocytic Lymphohistiocytosis

RFT: Renal Function Tests

EBV: Epstein Barr Virus

PUO: Pyrexia of Unknown Origin

FNAC: Fine Needle Aspiration Cytology

AFB: Acid Fast Bacilli

ATT: Anti Tubercular Drugs

ANA: AntiNuclear Antibodies

FHL: Familial Hemophagocytic Lymphohistiocytosis

CHS: Chediak-Higashi syndrome

HSCT: Hematopoietic Stem Cell Transplantation

Case Presentation

Hemophagocytic Lymphohistiocytosis (HLH) is a rare immune disorder, characterised by uncontrolled hemophagocytosis and hypercytokinemia [1]. The incidence of HLH is 1.2/1,000,000 children per year [2]. HLH is of two types, primary and secondary. Primary HLH is associated with genetic defect in the immune regulation, while secondary HLH occurs in association with infections, malignancies, rheumatological or metabolic disorders.

The clinical features of HLH are very non specific which makes accurate early diagnosis difficult. Most cases present with fever, hepatosplenomegaly, lymphadenopathy, jaundice, liver dysfunction, pancytopenias, coagulopathy and neurological manifestations. According to the 2004 revised diagnostic guidelines for HLH, the diagnosis of HLH can be established if molecular diagnosis is consistent with HLH or five out of the eight criteria for HLH are fulfilled [3]. The diagnostic criteria include Fever, Splenomegaly, Cytopenias (affecting 2 of 3 lineages in the peripheral blood-Hemoglobin <90 g/L, in infants <4 weeks: Hemoglobin <100 g/L; Platelets <100 10⁹/L; Neutrophils <1.010⁹/L), Hypertriglyceridemia and/or hypofibrinogenemia (Fasting triglycerides >3.0mmol/L, Fibrinogen <1.5 g/L), Serum Ferritin ≥ 500µg/L, Hemophagocytosis in bone marrow or spleen or lymph nodes, Low or absent NK-cell activity (according to local laboratory reference) and soluble CD25 (i.e., soluble IL-2 receptor) > 2,400 U/ml. Prognosis of HLH depends on timely diagnosis and prompt initiation of treatment. The condition has high morbidity and mortality and the median survival without treatment is estimated to be less than 2 months [4].

Case series:

We present a series of four cases of HLH, presenting with varied clinical features and different etiologies during a period of 1 year from Jan-Dec 2017.

Case 1: A 17 year old boy presented with history of fever of 1 week, jaundice from 3 days and decreased urine output since 1 day. On examination he was hemodynamically stable, had pallor, icterus and edema with hepatosplenomegaly. Investigations revealed hematuria with abnormal RFT (Renal Function Tests). A diagnosis of Weils Disease was considered and treated. However his RFT worsened requiring hemodialysis. He recovered from renal failure but fever persisted for three more weeks' inspite of antibiotics and

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antimalarials. A diagnosis of fever of unknown origin was made and worked up further. He developed generalised hyper pigmented rash. Investigations revealed pancytopenia, hypertriglyceridemia and very high serum ferritin levels (12000µg/litre). A provisional diagnosis of HLH was made. Bone marrow examination revealed hemophagocytosis. Genetic markers for HLH were negative and EBV (Ebstein Barr Virus) Ig G & Ig M was negative. Child was started on chemotherapy. He became afebrile after 1week, ferritin levels decreased and liver and spleen size was reduced at follow up. A diagnosis of secondary HLH was made, the cause of which could not be ascertained.

Case 2: A 14 year old boy presented with history of fever of 15 days. On examination child had significant left cervical lymphadenopathy, pallor and hepatosplenomegaly. All base line Investigations were normal and hence worked up for PUO (Pyrexia of Unknown Origin). Chest roentgenogram revealed mediastinal widening. Mantoux test and sputum for AFB (Acid Fast Bacilli) were negative. Sonogram of chest and abdomen showed mediastinal and para-aortic lymphadenopathy. FNAC (Fine Needle Aspiration Cytology) of lymph node showed reactive lymphadenitis. Bone marrow aspiration and biopsy revealed hemophagocytosis and acid fast bacilli. There was pancytopenia, hypertriglyceridemia and elevated ferritin levels. A diagnosis of HLH secondary to tuberculosis was made. He was started on ATT (Anti Tubercular Drugs) and chemotherapy. After one month, fever recurred with increasing size of lymph nodes. Repeat lymph node biopsy showed T Cell lymphoma. A final diagnosis of Secondary HLH due to T cell lymphoma with disseminated tuberculosis was made and chemotherapy was continued. He is on regular follow up and is improving. Genetic markers for HLH were negative.

Case 3: A 7 year old girl presented with fever since 2 months, abdominal pain and distension since 2 weeks. On examination child had pallor, bilateral pitting pedal edema, bilateral pleural effusion and moderate ascites with hepatosplenomegaly. Baseline investigations revealed pancytopenia. ANA (AntiNuclear Antibodies) profile was negative. Sonogram Abdomen revealed multiple tiny granulomas in the liver and spleen. Bone marrow biopsy showed macrophages with hemophagocytosis and erythroid hyperplasia. Child also had hypertriglyceridemia and elevated ferritin levels. Liver Biopsy revealed hepatic T cell Lymphoma and Genome sequencing was positive for HLH. Hence diagnosis of Primary HLH with Hepatocellular

T Cell Lymphoma was made and started on chemotherapy. However child succumbed

Case 4: A 9 year old girl presented with history of recurrent fever since six months. On examination child had pallor, diffuse patchy hypopigmentation of skin and silvery hair. Systemic examination revealed significant splenohepatomegaly. There was a history of similar skin changes among other family members. Baseline investigations revealed pancytopenia. Peripheral smear showed microcytic hypochromic anemia and neutrophils with no lysosomal inclusions. Light Microscopy of hair showed irregular arrangement of small and large clumps of melanin- suggestive of Griscelli syndrome. With this background of pigmentary dilution, fever, pancytopenia and splenohepatomegaly child was investigated for HLH. Child had hypertriglyceridemia and elevated ferritin levels. Bone marrow biopsy revealed hemophagocytosis. A diagnosis of primary HLH with Griscelli Syndrome type II was made. The child was lost for follow up. The detailed investigation of all the four cases are shown in (Table 1)

Discussion

HLH is a disorder of immune regulation. It is characterised by impaired activation of T lymphocytes following stimulation by immune responses. There is release of large amount of inflammatory cytokines that promote macrophage infiltration and cytokine network formation. This hypercytokinemia along with massive proliferation, migration and infiltration of macrophages into various organs results in progressive organ dysfunction and death [5].

Scott and Robb-Smith, first described this condition in 1939 as a disorder associated with hemophagocytosis. In 1952, Farquhar and Claireaux described a familial form of the disease [6-7]. HLH has an incidence of around 1 in 3000 in pediatric hospital admissions.² Males and females are found to be equally affected though a male preponderance is seen in adolescents.

HLH is broadly classified into primary and secondary HLH. Primary HLH or Familial hemophagocytic Lymphohistiocytosis (FHL) is an autosomal recessive disease and has an incidence of around 1:50000 live-born children. There are five different subtypes of FHL, type 1 to type 5 (FHL types 1-5). It is also found to be associated with certain primary immunodeficiency disorders like Chediak-Higashi syndrome (CHS-1), Griscelli syndrome type 2 (GS-II), Hermansky-Pudlak syndrome type 2 and X-linked proliferative syndrome (XLP-1)

Case Number	1	2	3	4
Age at Diagnosis	17 Yrs	14 Yrs	7 Yrs	9 Yrs
Gender	Male	Male	Female	Female
Clinical presentation	Hepatorenal syndrome	PUO	PUO with massive hepatosplenomegaly and ascites	Griscelli syndrome with PUO
Fever	7 days	15 days	2 months	6 months
Splenomegaly	Present	Present	Present	Present
Pancytopenia	Present	Present	Present	Present
Hypertriglyceridemia	445 mg%	207 mg%	325 mg [^] %	500 mg%
Liver Function Tests	Impaired	Normal	Normal	Normal
Serum Ferritin levels	1200microgm/L	1435	1006	156
Fibrinogen	low	Low	Low	Low
Hemophagocytosis in bone marrow	Present	Present	Present	Present
EBV/ Parvo virus B19	Negative	Negative	Negative	Negative
Genetic markers / exome sequencing	Negative	Negative	Positive for perforin gene defect	Not done
Associated Infections or Malignancy	Nil	Tcell lymphoma, Mycobacterium tuberculosis	Hepatic T cell lymphoma	Nil
Outcome	Recovered after chemotherapy	Improving on chemotherapy	Death	Lost for follow up

Table 1: Clinical and diagnostic profile of children with HLH

[8]and the overall prevalence of HLH in immunodeficiency syndrome is said to be 6%. Defective genes controlling the function of cytotoxic T-lymphocytes and NK -cells is said to be the cause of immune dysregulation in primary HLH. Mutations in the perforin gene is the commonest gene defect identified in FHL, accounting for 58% Primary HLH typically presents in infancy or early childhood. Of the two primary cases of HLH seen in our case series, the incidence was at a higher age of 7yrs and 9 yrs respectively. Genome sequencing showed defect in perforin gene in one child with HLH due to hepatic T cell lymphoma.

Secondary HLH on the other hand occurs in association with viral infections, tuberculosis, malignancies like non Hodgkin's lymphoma and T cell lymphomas, rheumatological disorders like systemic lupus, juvenile rheumatoid arthritis and some metabolic diseases [9].

Viral and other infections like tuberculosis are found to be associated with secondary HLH in 29% of cases, leishmaniasis in 20%, malignancies in 27% and rheumatological disorders are associated in 7% cases [5]. In our case series, one case of secondary HLH was found to be associated with T cell lymphoma and one case was found to have no known associated illness despite all work up. In a study by Pallazi et al, 42% had no known causes [10].

Clinically, HLH is associated with non specific symptoms usually presenting as PUO with splenomegaly and cytopenias. All children in our series presented with persistent fever and fulfilled 5 of the eight diagnostic criteria. Clinically, one of our cases had significant hepatic derangement and renal involvement along with generalised pigmentary changes. Another case had massive hepatosplenomegaly and as cites. None of our cases had CNS involvement which was found to be present in 62% of patients in the HLH-94 study by Henter JI et al [2].

Initial therapy for HLH consists of a combination of immunosuppressive therapy and pro-apoptotic chemotherapy (etoposide). Children with primary HLH need to undergo Hematopoietic Stem Cell Transplantation (HSCT) after the initial therapy. Mortality due to HLH was found to reduce from 95% to 30-35% with early therapy [1].All of our patients were treated with etoposide and steroids and both children with secondary HLH responded well to treatment. Of the two children with primary HLH, one due to hepatocellular lymphoma succumbed to the illness and the other child diagnosed as Griscelli syndrome was lost to follow up.

Conclusion

HLH should always be considered as a differential diagnosis in children presenting with fever of unknown origin, hepatosplenomegaly, pancytopenias, liver dysfunction and coagulopathy. Genetic testing should be done in all cases of HLH as the treatment modality of primary and secondary HLH differs. Also it helps in determining the prognosis. Secondary HLH in general has better prognosis and early diagnosis and treatment reduces mortality. Further studies are required from India to know the genetic pattern and the response to treatment. Also, greater awareness needs to be created among health professionals about HLH to promote early diagnosis and treatment.

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