Rare case of hemophagocytic lymphohistiocytosis: A case report

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ABSTRACT
A two-month old infant was admitted to our hospital with history of fever and cough. He was active and playful with normal systemic examination. He was started on antibiotics because the C-reactive protein (CRP) was high. Over the next few days he deteriorated with persisting fever, altered sensorium and hepatomegaly. Inspite of using third line antibiotics, the CRP kept increasing and the child showed no signs of improvement. A possibility of Hemophagocytic Lymphohistiocytosis (HLH) was considered. Ferritin was high and so the child was referred to a tertiary centre for further treatment. Bone marrow biopsy confirmed the diagnosis of HLH. HLH is a clinical syndrome of hyper inflammation, and uncontrolled and ineffective immune response. It could be primary where genetic mutations have been demonstrated or secondary to infection, malignancy or metabolic condition. Criteria have been laid done for the diagnosis of HLH. This condition should be considered when there is continued deterioration in spite of maximal supportive care.

Key words: hemophagocytic lymphohistiocytosis, infant, C-reactive protein

INTRODUCTION
Hemophagocytic Lymphohistiocytosis (HLH) describes a clinical syndrome of hyperinflammation resulting in uncontrolled and ineffective immune response. It may be primary or secondary HLH. Primary HLH is better defined as “genetic” encompassing both the familial hemophagocytic lymphohistiocytosis (FHL) and also HLH occurring in association with Chediak-Higashi syndrome, Griscelli syndrome type 2 and X-linked lymphoproliferative disorder¹. FHL is inherited as an autosomal recessive manner. The incidence is of 0.12 cases/100,000 children/year. The incidence is higher in areas where parental consanguinity is common². About 80% of the cases present before one year of age but only 10% are symptomatic in the neonatal period³. Five mutations leading to FHL have been identified and the underlying genetic defect described in four of these. Secondary HLH is seen in infection, malignancy, auto inflammatory and metabolic conditions¹.

Defects in the cytotoxic granzyme pathway may prevent efficient removal of the antigen or antigen presenting cell resulting in ongoing stimulation of the immune response leading to hypercytokinemia and continued expansion of population of histiocytes and activated cytotoxic T lymphocytes. High levels of IFNγ have been found in the serum of HLH patients⁴.

Secondary HLH can present at any age. It has more variability in severity and outcome, although the clinical picture may be identical to primary HLH. It is seen in the context of infection, underlying autoimmune disorders (where it is often termed Macrophage Activation Syndrome, MAS), some metabolic disorders and malignancy. HLH is reported to occur with a wide variety of infections, including bacterial, viral, protozoal and fungal infections⁵,⁶. Many clinical episodes of primary HLH are also triggered by an acute infection⁷. Herpes viruses, in particular EBV, are amongst the most common infections associated with HLH in children and young adults. The majority of the patients with EBV-HLH have a prolonged atypical infectious mononucleosis-like course but some will develop an aggressive
rapidly fatal primary EBV infection.

HLH is also seen in association with a number of rheumatic diseases like SLE, systemic onset JIA and Kawasaki disease. Clinical features are often similar to those in primary HLH but laboratory findings may be blurred by the preceding high levels of inflammatory markers associated with the underlying diagnosis. The clinical presentation of HLH in children can be varied and mimic the clinical features of sepsis, malignancy and autoinflammatory disorders. In order to improve the diagnosis of HLH, the Histiocyte Society published diagnostic guidelines in 1991, which were expanded in 2004. As per the revised criteria, five of the eight criteria are required to fulfill a clinical diagnosis of HLH, although patients with a molecular diagnosis, that is, one of the known FHL mutations, do not necessarily need to fulfill the diagnostic criteria.

The diagnosis of HLH can be established if either 1 or 2 below are fulfilled

A molecular diagnosis consistent with HLH
Diagnostic criteria for HLH fulfilled (5 out of 8 criteria below):
Fever
Splenomegaly
Cytopenias (affecting >2 of 3 lineages in peripheral blood)
Hemoglobin <9 g/dl (in infants <4 weeks: Hb<10 g/dl)
Platelets <100000
Neutrophils <1000
Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglycerides >3 mmol/l
Fibrinogen <1.5 g/l
Hemophagocytosis in bone marrow or spleen or lymph nodes
No evidence of malignancy
Low or absent natural killer cell activity
Ferritin >500 µg/l
Soluble CD25 >2400 U/ml

Ferritin estimation is routinely available in the laboratory. Ferritin levels >500 µg/l are considered significant, though >10000 µg/l is found to be 90% sensitive and 96% specific for the diagnosis of HLH. Natural killer cell activity and soluble CD25 level estimation can be done only in specialized laboratories. Soluble CD25 has been useful in the diagnosis of MAS in systemic onset JIA.

Fever, hepatosplenomegaly and cytopenias are the cardinal features that should raise a doubt of this condition in the pediatrician’s mind. In addition to this, continued deterioration inspite of maximal care will almost confirm the diagnosis. The presentation could be acute or insidious. Hyperferritinemia, raised transaminases, hypofibrinogenemia and hypertriglyceridemia are suggestive laboratory features. In up to 30% of cases, neurological symptoms and signs like ataxia, encephalopathy, irritability, cranial nerve palsies and seizures are seen at presentation. Fever may be absent in the neonatal period.

Without treatment, familial HLH is often rapidly fatal and the mortality for secondary HLH often exceeds 50%. The aim of therapy is to interrupt the amplification cascades of cytokines and suppress the hyperinflammation. Treatment options include a pro-apoptotic chemotherapy-based regimen as per the HLH protocols of the Histiocyte Society or a more targeted immunotherapy approach. A number of studies have reported successful hematopoietic stem cell transplant (HSCT) leading to cure of HLH. For cases associated with acute infection, treatment targeting the infecting organism is recommended but may not be sufficient in isolation to resolve the condition. EBV- HLH can be managed successfully with corticosteroid or intravenous immunoglobulin but studies in Japan have shown better survival with Etoposide. Antiviral therapy may be used to decrease the viral trigger. Isolated corticosteroid therapy and intravenous immunoglobulin therapy have both been used in MAS.
CASE REPORT
Our case was a 2-month old neonate who was admitted with history of fever and was started on antibiotic as the C-reactive protein (CRP) was high, suggesting a bacterial infection. Clinical examination had revealed a congested throat and the rest of the systemic examination was essentially normal. The child did not show a favorable response to the treatment that was initiated and, in fact, started having altered sensorium and respiratory distress. Clinical examination at this stage revealed a child who looked toxic and had a firm liver which kept increasing in size with splenomegaly. Repeat CRP showed a rising trend with thrombocytopenia and a falling hemoglobin level with raised transaminases, which warranted a change in antibiotic. Ultrasound of the liver showed a few cysts in the liver and chest X-ray revealed mild right sided effusion, while the blood culture and sensitivity did not show any growth. Change of the antibiotic did not alter the clinical status of this child. A possibility of a fungal infection was considered and it was decided to add antifungal therapy. Blood cultures which were repeated did not show any positive results. Because of the continued downhill course, an infectious disease specialist’s opinion was sought. The possibility of HLH was thought of and blood samples sent for ferritin level estimation. The ferritin levels were reported as high and so the baby was transferred to a tertiary center for further management. A bone marrow aspiration was done, which confirmed the diagnosis of HLH with no evidence of malignancy. He was started on chemotherapy after the seriousness and prognosis of the condition were explained to the parents. The child died after 2 days of chemotherapy. Genetic tests performed for the other family members were negative.

DISCUSSION
This case fulfilled 5 out of 8 criteria for the diagnosis of HLH. Fever, splenomegaly, cytopenias, hyperferritinemia and hemophagocytosis were the five criteria which were positive in this child. There has been criticism of the HLH diagnostic criteria as being too nonspecific and encompassing many patients on the pediatric intensive care unit with systemic inflammatory response syndrome (SIRS) and multiorgan dysfunction (MODS)
. This child had all features consistent with a diagnosis of sepsis and so he was started on antibacterial therapy. Since he did not respond to the best of antibiotics and supportive care, the suspicion of HLH was raised. This is the most important feature of any patient with HLH that has been highlighted by all the authors. Patients presenting in acute state to the general pediatrician or pediatric intensive visit with a clinical picture of likely sepsis (fever, laboratory evidence of inflammatory response, coagulopathy and thrombocytopenia) should be appropriately investigated and managed for sepsis, but the possible diagnosis of HLH should be borne in mind, particularly in the child who deteriorates despite maximal therapy. Increasing liver size with raised transaminases is a well-documented form of presentation of HLH which was seen in our index case. In addition up to 30% of cases can present with neurological symptoms and signs. This child did have encephalopathy which was a marked clinical feature during his stay in the hospital. The possibility of meningitis was also thought of and an Lumbar puncture (LP) performed. Unfortunately this was traumatic. Repeat LP could not be done because of the thrombocytopenia.

HLH has been described in association with a wide variety of infections. Though a bacterial infection was suspected in this child, all blood cultures were negative. Tests for viral causes were not undertaken as a viral etiology was not suspected. In this case, a possibility of a bacterial sepsis was entertained all along and so tests for EBV or herpes virus were not ordered.
Other authors have commented that Herpes viruses, and in particular, Epstein Barr Virus are among the most common infections associated with HLH in children and young adults. Ferritin is a commonly available investigation in most of the laboratories and so this could be done in our laboratory as well, which helped us to pursue the diagnosis of HLH more intensively. In conclusion, a possibility of HLH has to be taken into accounting any child who does not show the expected response to the therapy that has been initiated. Unless there is increased awareness of this condition, many cases may go undetected. Further research into the immunology and molecular diagnostics of HLH may help to identify children at risk, thus allowing for early detection and treatment and hopefully in the future for possible prevention of this condition.

REFERENCES


