EBV-associated Hemophagocytic Lymphohistiocytosis with Spontaneous Regression

A 9-year-old boy, previously healthy, was referred to our center with 10 days of fever, weakness, epistaxis and purpura. Examination revealed a febrile child who had marked pallor; petechiae over limbs and trunk; 1-1.5 cm multiple sub-mental lymph nodes; 3 cm hepatomegaly and 5 cm splenomegaly below costal margins respectively. Investigations (*Table I*) showed pancytopenia with lymphocytosis; elevated ALT and AST; repeated blood cultures were sterile. Bone marrow aspiration (BMA) revealed dyserythropoiesis and several histiocytes, some of which were exhibiting erythrophagocytosis suggestive of hemophagocytic lymphohistiocytosis (HLH). Further investigations revealed corroborative evidence of HLH in the form of elevated serum LDH, triglyceride and ferritin levels. Hepatitis virus serology was suggestive of an old infection with hepatitis B virus. Serology for Ebstein Barr Virus (EBV) was suggestive of recent infection. Serum immunoglobulins revealed mild reduction in IgA and IgM levels. Thus final diagnosis was EBV associated HLH. Patient showed remarkable clinical improve-ment with supportive care including intra-venous antibiotics, platelet and blood trans-fusions. Within a week, he was asymptomatic and follow-up showed gradual improvement with normalization of bio-chemical abnormalities and BMA at 6 weeks. At 15 months of follow-up, he remains asymptomatic.

HLH is a disorder of mononuclear phagocytic system characterized by proliferation and activation of histiocytes and macrophages. HLH comprises primary HLH (familial or hereditary HLH) and secondary HLH(1). Secondary HLH could be due to infections(2) which is termed as infection-associated hemophagocytic syndrome (IAHS); rheumatic disease and malignancies. HLH is an uncommon manifestation of many common tropical infections such as tuberculosis, leishmaniasis and salmonella. IAHS has a fatality rate of more than 50% in children. EBV-HLH is the most common reported IAHS resulting in severe disease. Clinical features of EBV-HLH include high fever, hepato-slenomegaly, cytopenia, liver dysfunction, coagulopathy, lipid changes because of hypercytokinemia and organ infiltration by phagocytosing histiocytes(3).

Specific treatment includes using immuno-suppressants such as steroids and cyclosporine A and cytotoxic agents such as etoposide. For FHLH and relapsed/aggressive EBV-HLH, stem cell transplantation is the only curative option. The main causes of early death are hemorrhage and infection. The initial management of EBV-HLH is aimed at reducing the likelihood of this early death, which includes careful monitoring of hemostatic parameters, blood products administration, treatment of infection and prompt introduction of cyclosporine A. The decision whether to treat a child with presumed secondary HLH with specific drugs should depend solely on the clinical condition of the patient and associated laboratory changes(4). The progression to lymphoma or leukemia also seems to be a special problem in these cases(5); which is why the patient is, and will be on continued follow-up and monitoring.

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TABLE I–*Investigation Profile of the Patient*

A. Primary Investigations	
Hemoglobin	6.4 g/dL
Platelet	41, 000/m^3
White Blood Cell	1900/m^3
Differential	N18, L81, M1; anisocytosis and macrocytic anemia, nucleated RBC 1-2/100 WBC; no blasts.
Renal Function Tests	Normal
Aspartate aminotransferase	196 IU/L (N: <50 IU/L)
Alanine transferase	134 IU/L (N: <50IU/L)
Chest Radiograph	Normal
USG Abdomen	Hepatosplenomegaly with no focal lesions
B. Investigations for corroborative evidence of HLH	
DIC	Profile Normal except thrombocytopenia
Fibrinogen	380 mg/dL (200-450 mg/dL)
Lactate dehydrogenase	973 U/L (N: 100-190 U/L)
Triglyceride	459 mg/dL (N: 50-150 mg/dL)
Ferritin	2450 ng/L (N: 15-400 ng/L)
C. Investigations for corroborative evidence of HLH	
Hepatitis B Surface antigen	Positive
Hepatitis B core IgM antibody	Negative
Hepatitis C Serology	Negative
Parvovirus IgM	5.8 U/mL (N: <17 U/mL)
Cytomegalovirus IgM	0.35 A.I. (0-0.9)
Human immunodeficiency virus	Negative
EBV IgM	40.63 U/L (N: <12U/L)
EBV IgG	106.6 U/L (N: <12U/L)
IgG	2860 mg/dL (N: 960-1968 mg/dL)
IgA	90 mg/dL (N: 125-380 mg/dL)
IgM	65 mg/dL (N: 90-242 mg/dL)

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Unusual Congenital Cystic Adenomatoid Malformation of the Lung: A Diagnostic Dilemma

Congenital cystic adenomatoid malformation (CCAM) of the lung represents an abnormal hamartomatous proliferation of bronchioles at the cost of alveoli(1). In the developed world, CCAM is usually diagnosed antenataly. The natural history of this antenataly diagnosed condition may be very varied. It may occasionally progress to non-immune fetal hydrops, or it may decrease in size or may even regress(2). The majority would however present with respiratory distress at birth. It may occasionally present as recurrent chest infections in childhood or later adulthood(3).

We report our experience with a neonate, aged 3 weeks, referred to us for progressively increasing respiratory distress since birth. No antenatal workup was available. The clinical and pre-operative radiological picture of the patient mimicked congenital diaphragmatic hernia (*Fig. 1*) for which he underwent laparotomy, which revealed normal abdominal anatomy with intact diaphragm. The follow-up chest radiograph showed hyper-inflated lung with mediastinal shift and was suggestive of congenital lobar emphysema. Keeping in mind the significant respiratory distress, a left thoracotomy was performed few hours later that revealed multiple cysts in left lower lobe of lung. Left lower lobectomy of lung was done. The histopathology of resected specimen however came as surprise; it was reported as CCAM. The child had stormy post-operative period. He required ventilatory and ionotropic support and succumbed to persistent pulmonary hypertension and sepsis on l0th post-operative day.

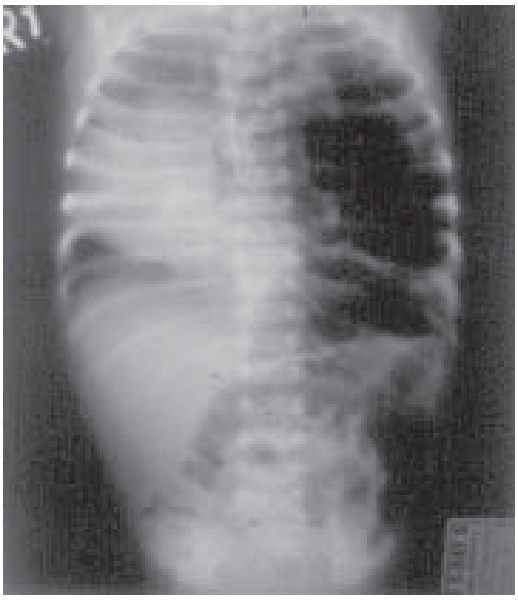

Fig. 1. Chest roentgenogram at first presentation that was suggestive of CDH.