

LETTER TO EDITOR (VIEWERS CHOICE)

NEONATAL HEMOPHAGOCYTTIC LYMPHOHISTIOCYTOSIS (HLH)

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A 28 days old female child presented with fever for 3 days followed by fullness of abdomen. She was born at term by non-consanguineous marriage. Elder sibling had died at 1 ½ months of age due to septicemia. On presentation, the child was dull and lethargic, had hepatosplenomegaly with few purpuric spots on the abdomen. Antibiotics were started in view of clinical suspicion of sepsis. Investigations showed hemoglobin 9.5g/L, white cell count (WBC) 5900 cells/cumm (neutrophils 19%), platelets 35,000 cells/cumm, serum bilirubin 18.6 mg/dl (direct 0.6 mg/dl), C-reactive protein (CRP) 5.51mg/L, prothrombin time (PT) > 100 sec and activated partial thromplastin time (APTT) >100 sec. Blood culture did not grow any organism. Ultrasound (USG) abdomen revealed hepatosplenomegaly with mild ascites. Babygram (x-ray of entire body) and CT scan head did not reveal any bony lesion. During the following week condition of the child deteriorated and a repeat blood count was done which showed a drop in hemoglobin to 7.5g/L, WBC decreased to 3000 cells/cumm (neutrophils 8%). Platelets dropped down to 20,000 cells/cumm, ESR was 60mm and there were atypical large mononuclear cells with moderate amount of foamy cytoplasm. Four days later a bone marrow aspiration was done which was suggestive of hypoplastic marrow with hemophagocytes. Serum ferritin was > 16500 ng/ml, triglycerides were 260 mg/dl. Serum bilirubin increased to 30.1 mg/dl (direct 16.7 mg/dl). At the time of doing flow cytometry total leucocyte count was 2,800 cells/cumm with 90% lymphocytes and there were 42% T cells (Normal range 50-72%), 6.3% B cells (Normal range 16-38%), 40% NK cells (Normal range 9-16%), 57% NK+ perforin (Normal range 80-90%). The child was started on steroids and intravenous immunoglobulin IVIG (2gm/kg) on day 5 but continued to deteriorate and expired on day 7 of admission.

The lymphoproliferative disorder of hemophagocytic lymphohistiocytosis (HLH) can be divided into two categories: primary (familial) hemophagocytic lymphohistiocytosis (FHL) and secondary HLH. The incidence of FHL is 1:50,000 births, with an equal gender distribution. (1) In contrast to secondary HLH, which may affect any age and may resolve spontaneously, FHL is seen primarily in children and is fatal if untreated. (1) Most cases of FHL are diagnosed before 2 years of age, and the disease may present in the newborn period. (2-4) The diagnostic criteria for HLH include fever for 7 or more days, splenomegaly, cytopenia of two or three lineages (unassociated with a hypocellular or dysplastic marrow), hypertriglyceridemia and/or hypofibrinogenemia, and histopathological evidence of hemophagocytosis in the bone marrow, spleen, liver, or lymph nodes. (5) Hepatomegaly, jaundice, lymphadenopathy, edema, and rash are also seen.

There can be central nervous system involvement with meningismus, seizures, encephalopathy, and/or spinal fluid pleocytosis. Cutaneous manifestations include erythroderma, generalized purpuric macules and papules and morbilliform eruptions. Neonates presenting with isolated thrombocytopenia or hepatic dysfunction, with other characteristic findings becoming evident subsequently, have also been reported. (4) Clinical and laboratory parameters fulfilled the criteria for the diagnosis of HLH. In view of the fact that one sibling had died of a septicaemic illness, a possibility of hereditary HLH was entertained, but since gene mutation studies could not be done it could not be proved.

Because neonatal HLH can be rapidly fatal without specific intervention, it is recommended to start a treatment when a high clinical suspicion exists and results of diagnostic studies are still pending. Stem cell transplant is the standard treatment for FHL, once remission is achieved on immuno-modulatory therapy. (6) However in our setup genetic diagnosis is not available and stem cell therapy is difficult, hence we used steroid with IVIG as a favorable response with IVIG has been observed. (7) Other therapies include combined use of etoposide, cyclosporine A, and corticosteroid. Intrathecal treatment is suggested for patients with central nervous system. When the HLH protocol is ineffective, anti-thymocyte globulin may be suggested. Genetic counseling and family planning is of utmost importance. Subsequent pregnancies should be closely monitored and offspring referred for genetic testing. Mutations in the perforin gene have been reported to be present in 20-40% of FHL. Perforin staining in cytotoxic cells by flow cytometry has been documented as a screening test to identify children with FHL. (6) Other tests for genetic analysis include mutations in the Munc13-4 and syntaxin 11 gene. (8)

Authors Contribution

PM, ST, YKR drafted the article. All authors critically appraised the manuscript for intellectual content.

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