Tuberculosis-associated Hemophagocytic Syndrome in Infancy

S BALASUBRAMANIAN
K KAARTHIGEYAN
V APARNA
S SRINIVAS*

ABSTRACT

An infant presented with prolonged fever, generalized lymphadenopathy, splenohepatomegaly, anemia and seborrheic dermatitis. Investigations including bone marrow findings confirmed the diagnosis of hemophagocytic syndrome (HPS) and the infant succumbed. Liver biopsy features of epitheloid granuloma and positive AFB culture of gastric aspirate confirmed the diagnosis of tuberculosis (TB). This rare association of HPS and tuberculosis in infancy is reported.

Key words: *Hemophagocytic syndrome, Infant, Infection associated Hemophagocytic syndrome, Tuberculosis.*

INTRODUCTION

Hemophagocytic lymphohistiocytosis, also called Hemophagocytic syndrome (HPS) is characterized by a dysregulated activation and proliferation of macrophages, leading to uncontrolled phagocytosis of platelets, erythrocytes, lymphocytes, and their hematopoietic precursors throughout the reticulo-endothelial system(1). So far 37 cases of tuberculosis-associated HPS have been reported with only 5 in pediatric population including 2 in infancy; and none from India.

*From the Department of Pediatrics, and *Division of Pediatric Gastroenterology, Kanchi Kamakoti CHILDS Trust Hospital, Chennai, India.*

Correspondence to: Dr S Balasubramanian, Senior Consultant Pediatrician, Kanchi Kamakoti CHILDS Trust Hospital, 12-A, Nageswara road, Nungambakkam, Chennai-34, TN, India. E-mail: sbsped53@sify.com

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CASE REPORT

A 52-day-old male infant, second born to parents of third degree consanguineous marriage, presented with fever from 25 days of life with skin lesions over the trunk and extremities. He was born after a full term normal delivery with a birth weight of 3 Kg. There was no significant illness in the antenatal period and there was no history of contact with tuberculosis. The infant was treated with intravenous antibiotics for 3 to 4 days and was reported to have 2 seizures before he presented to our hospital. On examination, the infant was febrile (101ºF), pale, acutely ill with extensive and severe seborrheic dermatitis over the trunk and extremities. Generalized lymphadenopathy was seen with a significant left axillary lymph node (>25 mm, matted and firm) and abdominal examination revealed moderate firm splenohepatomegaly (liver span of 10 cm and spleen palpable 6 cm below left costal margin). Examination of the other systems revealed no abnormalities.

The laboratory investigations observed at the initial assessment revealed microcytic hypochromic anemia (hemoglobin 6.9 g/dL), leukocytosis (59,500 cells/mm^3), thrombocytopenia (75,000 cells/mm^3), a shift to left in the granulocyte series in peripheral smear, raised erythrocyte sedimentation rate (68 mm/h), with markedly elevated levels of C-reactive protein (384 mg/L).

Liver function tests did not reveal abnormalities. Hypokalemia (3.2 mmol/L), hypocalcemia (5.4 mg/dL) with hypophosphatemia (2.3 mg/dL) and normal alkaline phosphatase level were observed. Routine urine analysis did not reveal significant abnormalities. Chest roentgenogram showed bilateral hyperaeration. Ultrasound cranium did not reveal any abnormality and sonogram of the abdomen showed splenohepatomegaly. The cerebro-spinal fluid analysis for cells, sugar and protein were normal. There was no growth in cultures of blood,

urine, CSF and bone marrow aspirate. Bone marrow aspirate revealed features of hemophagocytosis with reactive granulocytic hyperplasia. The baby was initially treated with intravenous ceftriaxone and packed cell transfusion.

Further laboratory work up revealed elevated levels of gammaglutamyl transferase (224 IU/L), lactate dehydrogenase (2133 IU/L), hypertriglyceridemia (218 mg/dL), and hyperferritinemia (1885 mcg/L). Serum IgG, IgM and IgA levels were normal. ELISA for HIV was negative. CD4/CD8 ratio was normal. Three consecutive samples of gastric aspirate were positive for acid-fast bacilli (AFB) and culture of gastric aspirate for AFB grew *Mycobacterium tuberculosis* on Lowenstein-Jensen medium. The strain was identified as human *Mycobacterium tuberculosis* based on microbiological studies (carried out at Tuberculosis Research Centre under ICMR, Chetpet, Chennai). Liver biopsy revealed epitheloid granuloma with caseating necrosis, typically consistent with tuberculous granuloma. Anti-tubercular therapy with 4 drugs–isoniazid (INH) 5 mg/kg/day, rifampicin 10 mg/kg/day, ethambutol 15 mg/kg/day, pyrazinamide 20mg/kg/day (2HRZE+7HR) regimen was started.

In view of persistent fever, hepatosplenomegaly, anemia, thrombocytopenia, elevated levels of triglycerides, lactate dehydrogenase and ferritin and features of hemophagocytosis in bone marrow, a diagnosis of Infection-associated hemophagocytic syndrome (IAHS) was made. Along with anti-tuberculosis therapy, intravenous immunoglobulin infusion (0.5 g/kg/day for 4 days) was also administered. The infant subsequently developed septic shock with progressive respiratory failure needing mechanical ventilation. The infant died due to ARDS 18 days after hospitalization. Chest *X*-rays of both the parents were normal. Further investigations to identify maternal tuberculosis could not be carried out due to lack of follow up.

DISCUSSION

Hemophagocytic lymphohistiocytosis is a rare and potentially fatal syndrome associated with a variety of genetic, malignant, autoimmune or infectious conditions(2). According to the Histiocyte Society Protocol entitled HLH 2004 (3), the diagnosis of HLH can be established if five out of following eight diagnostic criteria are fulfilled (*i*) fever (≥7 days), (*ii*) splenomegaly, (*iii*) cytopenia (≥ 2 lineages)–anemia (hemoglobin <9.0 g/dL), thrombocytopenia (<100,000 cells) and neutropenia (ANC <1000), (*iv*) hypertriglyceridemia (≥265 mg/dL) and/or hypofibrinogenemia (<1.5 g/L), (*v*) hemophagocytosis (bone marrow, spleen, lymph node), (*vi*) low/absent NK cell activity, (*vii*) hyperferritinemia (≥500 mcg/L), and (*viii*) increased soluble CD25 >2400 units/mL. In our case, six out of eight criteria were present.

The diagnosis of HPS can be difficult to make, because the symptoms of many patients do not have all the necessary criteria at presentation. Based on previous publications, it appears that TB associated HPS is more common in adults than in children. In the reported cases, pancytopenia was present in all at some point during the course of their illness, although a normal or raised total leukocyte count has also been reported. In our case leukemoid reaction was observed. In most pediatric cases, success of therapy was attributed to initiation of therapy early in the course of the illness.

Patients have been treated successfully with various immunomodulatory therapies, including dexamethasone, intravenous immunoglobulin, anti-thymocyte globulin, cyclosporin A, and etoposide-based chemotherapeutic regimens(1,4,5).

Only 2 cases of TB-associated hemophagocytic syndrome have been reported in infancy. Both had congenital tuberculosis(6,7), however this could not be proven in our case.

Contributors: SBS, SS were involved in case management. SS carried out the liver biopsy and interpreted it; KK, AV were involved in review of literature and preparation of manuscript. SBS will act as guarantor.

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Partial Trisomy 9q due to Maternal 9q/17q Translocation

SHEELA NAMPOOTHIRI
LAKSHMY R LAKSHMAN
ALKA ANILKUMAR
M V THAMPI*

ABSTRACT

Partial Trisomy 9q is a unique chromosomal anomaly with a distinctive phenotype. Only 5 cases have been reported in the literature till now. A large family with four affected children was studied in detail and was compared with the five previously reported cases. Determination of this novel balanced translocation in their family had helped us to offer prenatal diagnosis. This presentation is unique as even though partial trisomy 9q has been reported earlier with 9/17 translocations, our family is the first to have a translocation between q arms of chromosomes 9 and 17.

Key words: *Arachnodactyly, Camptodactyly, Contractures, Partial trisomy 9q.*

INTRODUCTION

Partial trisomy 9q is a distinct phenotype with severe psychomotor retardation, dolichocephaly, long fingers and toes, prominent beaked nose, deep-set eyes and camptodactyly(1,2). We present four children with this condition who are first cousins.

CASE REPORT

The proband (IV 5) was a 13 day old male baby weighing 2250 g born to a 30 year old second gravida mother by cesarean section. The parents were non consanguineous. On examination the baby had dolichocephaly, a prominent beaked nose with deep-set eyes, a small mouth, and ears with overfolded helices. The palate was narrow and high-arched. He fed poorly and had epiphora from both eyes due to associated trichiasis. He had prominent arachnodactyly. The fingers were flexed across the thumb bilaterally. He also had flexion contractures of both knees and left elbow. The limbs were extremely thin due to reduced muscle mass (dolichostenomelia). *X*- rays showed thin, osteoporotic long bones. He had bilateral undescended testes.

The trichiasis and flexion contractures improved gradually. At one year of age the only developmental

*From the Departments of Pediatric Genetics, and *Human Cytogenetics, Amrita Institute of Medical Sciences & Research Center, Elamakkara PO, Cochin 682 026, Kerala, India.*

Correspondence to: Dr. Sheela Nampoothiri, Department of Pediatric Genetics, Amrita Institute of Medical Sciences and Research Center, Elamakkara PO, Cochin 682 026, Kerala, India.
E mail: sheelaknpn@yahoo.co.in

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