CASE REPORT

CHEDIAK-HIGASHI SYNDROME IN ACCELERATED PHASE AT INITIAL PRESENTATION

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Abstract

Chediak - Higashi Syndrome (CHS) is a rare autosomal recessive disease which results from defective degranulation of primary lysozomal granules with delayed microbial killing. Most of the patients with CHS enter into an "accelerated phase" as in our case who manifested by fever, hepatosplenomegaly and lymphadenopathy leading to pancytopenia and bleeding disorders.

Key words: Chediak - Higashi Syndrome, oculocutaneous albinism

Introduction

Chediak-Higashi Syndrome (CHS) is a rare autosomal recessive disorder which possibly results from defective degranulation of fusion of primary lysozomal granules, with delayed microbial killing (1). The condition is characterized by partial oculocutaneous albinism, frequent pyogenic infections, abnormally large granules in the leukocytes and other granule-containing cells (including platelets, melanocytes, renal tubular cells, pneumocytes, gastric cells, hepatocytes, neuronal cells and fibroblasts). About 85% of patients with CHS enter into an "accelerated phase," manifested by fever, jaundice, hepatosplenomegaly, lymphadenopathy and widespread lymphohistiocytic organ infiltrates with hemophagocytosis, leading to pancytopenia, hypertriglyceridemia and hemodilution, and bleeding disorders secondary to low platelet and fibrinogen levels (2)(3).

After the first description of CHS to date, around 170 human cases have been mentioned in the literature worldwide (4). In India 8 cases have been reported. (5). We present a child with CHS and pancytopenia.

Case Report

A 4 years old boy with normal developmental history born of non-consanguineous marriage was admitted with history of abdominal distention and low grade fever for the past 7 months, itching all over the body for the past 3 months and swelling in the neck for 1 week. He had a history of diminished vision for few days 2 years back. At one year of his age he had enteric fever and no history of recurrent infections. He was the first sibling and the one year old younger sibling was apparently normal. There was no history of bleeding or contact with tuberculosis. Examination revealed silvery hair, severe pallor, anasarca, ecchymotic rashes on left cheeks, 3 non-tender submandibular lymphadenopathy 1.5cmx1.5cm and hypopigmented multiple macular lesions over the trunk, On systemic examination, there was hepatosplenomegaly. Ophthalmic examination revealed retinal detachment and pallor in both eyes. On investigation, hemoglobin was 2.0 g/dl, total leucocyte count was 4,500/cumm with 10% neutrophils and 90% lymphocytes. Peripheral smear revealed hypochromia, anisocytosis and fair number of macrocytes with reduced total leukocytes count and platelets. Few neutrophils and monocytes showed giant granules. Reticulocytes were 2%. Stool for occult blood was negative. Serum total protein and albumin was 5.8 and 4.2 gm/dl respectively. Prothrombin time was 13 seconds and INR was 1.45. Ultrasound abdomen revealed hepatosplenomegaly with ascitis. Chest X-ray showed non-homogenous patches and mantoux test was nonreactive. Lymph node biopsy was inconclusive. Blood culture did not show any growth. Malaria, sepsis and hemolytic anemia were ruled out. Serum ferritin was 532 ng/ml and there was mild hyperlipiedemia (cholesterol 192 mg/dl and triglycerides 186 mg/dl). The bone marrow aspirate revealed increase number of myelocytes and few myelocytes and neutrophils also showed giant pink cytoplasmic granules. Histocytes arranged in sheets with pale foamy cytoplasm and engulfing intact red blood cells were seen. Also seen were fragmented erythrocytes, both features consistent with CHS and haemophagocytic lymphohistiocytosis (HLH). Megakaryocytes were slightly decreased in number. Plasma cells were within normal limits. Reticulum cells were slightly increased in number. There were no haemoparacytes seen. The child was put on IV fluids and antibiotics. He was infused 4 packed cell transfusions and the last haemoglobin was 8.8gm/dl. During the course of the hospital stay, fever reduced in intensity and itching subsided. He was treated with 200mg of ascorbic acid per day. Bone marrow transplantation was planned and child was referred to higher center.

Discussion

In 1952, Chediak described the full clinical and hematological features in four members of the same family. All the children were similarly affected, exhibiting pale hair and photophobia, with frequent infection and lymphadenopathy, and all died at an early age. It was then that the large inclusion-like granules were noted in the blood and bone marrow granulocytes. In 1954, Higashi described the same features in a Japanese infant, and added that these granules gave a positive peroxidase reaction (1). Hence the term Chediak-Higashi Syndrome.

The primary defect is caused by mutation of the lysosomal trafficking gene2, first recognized in 1996 as the CHS1 (LYST) gene and is located on bands 1q of chromosome 1 (4). The protein (3801 amino acids) encoded by Beige gene on chromosome 13 and CHS1/LYST gene is involved in the vesicular trafficking but the mechanism remains unknown (6). Both neutrophil and monocytes in peripheral smear and few myelocytes in bone marrow show giant granules. These giant granules from CHS neutrophils originate from azurophil granules but not from the specific and gelatinase granules (7).

The present case presented with accelerated phase of CHS. Whether accelerated phase is a neoplastic process or expression to a viral reaction is controversial. Merino et al (8) demonstrated elevated titers to Ebstein-Barr virus in patients with CHS. The

descriptive term "accelerated phase" originated in 1964 and is still in use as the pathophysiology of the process remains unknown. The molecular basis of CHS remains unknown as well. Functional studies suggest that genetic heterogeneity with defect in the microtubular function is suspected. The identification of the defective gene suggests that the disorder is in the organellar membrane docking and fusion. The clinical onset of the "accelerated phase" of CHS may occur shortly after birth, or may be delayed for years, but it invariably leads to death. Fukai et al (1) reported a case in a Japanese female infant of consanguineous parents presenting with hyperpigmentation of sun-exposed areas of skin, who enjoyed good health until 12 years of age, when she developed pneumonia with hepatosplenomegaly.

CHS is a disease of infancy and early childhood, and few patients survive into their teenage years. Although many CHS cases reported have been offspring of consanguineous marriage, other cases (2) have also been reported in children of unrelated parents as in our case. The homozygous children are usually manifested by partial oculocutaneous albinism with occasional pale retinae, translucent irides and photosensitive dermatitis, and later with recurrent pyogenic infection, including respiratory tract, mouth and cutaneous infection. Increased bleeding tendency is also a frequent feature of these children (4).

Reported cases usually had recurrent pyogenic infection. The present case didn't have any history of recurrent pyogenic infections. But the accelerated phase was the initial presentation in our case. Our case had silvery hair, albino macular spots and ecchymotic patches with other features of accelerated phase.

Neurologic involvement is variable but often includes peripheral neuropathy. The mechanism of peripheral neuropathy in CHS has not been completely elucidated. Both the axonal type and the demyelinating type of peripheral neuropathy associated with CHS have been reported. Approximately half of the patients develop neurological manifestations like peripheral neuropathy, long tract signs, seizures and mental impairment (4). Our patient didn't have any neurological problem probably because of the early presentation. Defective melanization of melanosomes occuring in oculocutaneous albinism (9) can explain the vision loss in this child.

Our patient didn't have any clinical improvement after the high dose ascorbic acid therapy. Since the disease is usually lethal in the first decade, bone marrow transplantation of HLA matched donor is the only curative approach.

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