Case Report

Chediak-Higashi Syndrome: Report of a Case with an Accelerated Phase and Review of Literature

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ABSTRACT

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by partial albinism, recurrent pyogenic infection and large granules in all granule-containing cells.

We present a case of 1 1/2 year-old non-Kuwaiti boy who presented in the accelerated phase of CHS with fever, pancytopenia, lymphadenopathy and hepatosplenomegaly.

KEY WORDS: accelerated phase, bone marrow transplantation (BMT), Chediak-Higashi syndrome (CHS)

INTRODUCTION

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by severe immunodeficiency, oculocutaneous albinism, bleeding diathesis, recurrent infections, progressive neurological defects and lymphoproliferative syndrome.

Patients with CHS enter an accelerated phase that often results in death. The first accelerated phase of CHS may occur shortly after birth or several years later. Most patients undergo a variable period of recurrent infections before going into the accelerated phase[1].

Typical laboratory findings are the presence of giant cytoplasmic granules in all granule-containing cells in peripheral blood and in the bone marrow. The treatment of choice for CHS is bone marrow transplantation and should be proposed as early as possible before the accelerated phase of disease develops[2].

CASE REPORT

An 18-month-old non-Kuwaiti boy presented with a two week history of fever and cervical lymphadenopathy not responding to oral antibiotics given in a private clinic. His parents are consanguineous with no family history of blood diseases or similar conditions. He was admitted to several hospitals in Kuwait since the age of four months for mild recurrent infections.

On physical examination he looked well-grown with fair skin and grey hair. In addition, he had pallor, jaundice, bilateral cervical lymphadenopathy, hepatomegaly (7 cm below RCM) and splenomegaly (5 cm below LCM). No evidence of meningeal signs or neuropathy was noted.

Investigations showed pancytopenia. Results of investigation were as follows: Hb 8 gm/dl, WBCs 5.9x10⁹/l, neutropenia (ANC 400), platelets 60 x 10⁹/l. Peripheral smear revealed giant granulation of neutrophils, monocytes and lymphocytes (fig. 1). Transaminases; ALT 209 u/l, AST 190 u/l, total bilirubin 180 umol/l with direct 154 umol/l, coagulation profile; PT 19.1 sec, PPT 50.3 sec, ratio 1.63, LDH 250 u/l, triglycerides 3.5 mmol/l, and ferritin 2500 ng/ml. No growth of micro-organisms was observed in either urine or blood cultures, and the IgM antibodies against Ebstein Barr virus (EBV) and cytomegalovirus (CMV) were positive.

Bone marrow smear showed giant granules in the cytoplasm of granulocytic series (fig. 2) with accentuation of peroxidase-positive granules. There were no abnormal blast cells (fig. 3). Based on the clinical presentation and hematological findings a diagnosis of accelerated phase of CHS was made.

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The patient was treated with empirical antibiotics, gancyclovir, high doses of methyl prednisolone, prednisolone and intravenous immunoglobulin. Improvement of clinical well being, pancytopenia and reduction in hepatosplenomegaly were noticed as a clinical response to the therapy. Since the father is HLA-identical to the patient, bone marrow transplantation (BMT) was highly recommended. Unfortunately the procedure is not available in Kuwait and could not be done abroad because of financial reasons.

**DISCUSSION**

The Chediak-Higashi syndrome (CHS) is a rare but global disease. It is inherited as an autosomal recessive disease with equal sex distribution affecting predominantly phagocytes and melanocytes. Apart from human beings, this disease has been recognized in aleutin mink, beige mice, cats, cattle and killer whales. A high proportion of CHS cases reported have been offspring of consanguineous marriage as in our case, although other cases have also been reported in children of unrelated parents. CHS is a disease of infancy and early childhood. Children with CHS usually manifest by partial oculo-cutaneous albinism and later with recurrent pyogenic infections including those of the respiratory tract, mouth and skin. Increased bleeding tendency is also a frequent feature in these children. However, in more than 85% of cases the disease remains mostly quiescent in early childhood with minor infections until it changes to the accelerated phase characterized by non-responding fever, pancytopenia, coagulopathy, peripheral neuropathy and widespread lymphohistiocytic organ infiltrates leading to infection and death. The first accelerated phase may occur shortly after birth or several years later, and the average life span of affected children without BMT is six years. Neurological manifestations such as peripheral neuropathy, long tract signs, seizures and mental impairment occur in approximately half of the patients. Our case did not have such a manifestation, probably due to the early detection. Subtle pigmentary abnormalities with normal eyes and absence of family history of the disease in our case made the clinical diagnosis difficult.

The first clue to the diagnosis was the laboratory reports of giant granules in the leucocytes of the peripheral blood smear which were confirmed by bone marrow examination with accentuation of peroxidase stain. Characteristic giant granules in all leucocytes result from abnormal fusion of both lysosomal azurophil (primary) and specific (secondary) granules which contain CD65 and myeloperoxidase, an enzyme characteristic of primary and secondary granules. These abnormal inclusions in CHS neutrophils are unable to adequately metabolize and digest microbes leading
to recurrent infections in early childhood[8]. In melanocytes, the defective granules produce a dilute pigment which is responsible for partial albinism.

Though the common organism associated with infection in chronic stable phase of the disease are *S. aureus* and *Streptococcus supp.*. Ebstein barr virus (EBV) is implicated in the accelerated phase[9]. It is believed that the inability to clear the EBV infection leads to a state of constant lymphoproliferation, as seen in the phase of disease acceleration. The same virus may be responsible for the hemophagocytic syndrome[10].

The CHS gene was identified in 1996 and has been mapped onto chromosome 1q42-44, a region code for a protein[7]. However, its function remains unknown. Referring to a recent study, the results suggested that the CHS/beige protein interacts with at least two different partners and affects cellular events such as PtdIns (4,5) P2 localization, in addition to regulating lysosome size[11]. Moreover, a study showed the apparent allelic genotype-phenotype relationship among the various clinical forms of CHS. Homozygous protein-null alleles were associated with severe childhood CHS, and at least some homozygous disease mutant alleles were associated with clinically milder forms of the disorder[12].

Other immune-deficiencies can present clinical manifestations similar to those of CHS. Griscelli syndrome, described in 1978, was characterized by partial oculocutaneous albinism, cellular and humoral immuno-deficiencies, neurological deterioration and an accelerated phase similar to that described in CHS. However, the granular phenotype in the bone marrow is a clear indication of CHS[13].

The treatment of CHS is still controversial. Parenteral vitamin C administration in the stable phase may normalize neutrophil bactericidal activity, but it has little benefit in the accelerated phase[14]. In some patients, high dose methyl prednisolone with or without immunoglobulin may be effective. Chemotherapy with etoposide in association with steroid and intrathecal methotrexate can induce transient remission of the accelerated phase but relapses become less responsive to the treatment[15]. Receiving G-CSF maintenance treatment in case of CHS prevents further infectious episodes within a six months period according to a report[16].

Allogeneic bone marrow transplantation has been proposed as the only possible curative treatment when performed early before the onset of the accelerated phase. It corrects the immunologic status but does not affect pigment dilution[17]. Allogeneic bone marrow transplantation from HLA-matched sibling is the treatment of choice. If no matched family donor is available, an unrelated donor or placental blood graft is a good alternative. Without BMT, children with CHS usually die before the age of 10 years[18,19].

**CONCLUSION**

We suggest that peripheral blood film examination for abnormal giant granules in granulocytes is an essential investigation in all young children with frequent infection or who are suspected to have virus associated hemophagocytic syndrome or familial hemophagocytic lymphohistiocytosis. The early detection CHS cases can lead to BMT which is the only curative treatment of this disorder.

**REFERENCES**


