

Chediak-Higashi Syndrome Presenting in Accelerated Phase

Tanzeel Imran¹, Lubna Zafar², Madeeha Rehan¹, Aqsa Nasir⁴, Parveen Akhtar Tariq³ and Iffat Batool³

ABSTRACT

Chediak-Higashi Syndrome (CHS) is a rare autosomal recessive disorder, characterized by silver hair, recurrent infections, partial oculo-cutaneous albinism, mild coagulation defect and progressive neuropathy. The characteristic feature of CHS is the presence of huge lysosomes and cytoplasmic inclusions within different body cells like the white blood cells. The disease has an early onset but usually presents in an accelerated phase. We present a case of a 2 years old boy with high grade fever, bilateral cervical lymphadenopathy, hepatosplenomegaly, abdominal distention of 28 days duration. He was diagnosed with Chediak-Higashi syndrome in accelerated phase on the basis of clinical presentation, morphological findings on peripheral blood film and bone marrow aspirate.

Key words: Chediak-Higashi syndrome. Oculo-cutaneous. Albinism. Accelerated phase. Giant lysosomal inclusions.

INTRODUCTION

Chediak-Higashi Syndrome (CHS) is a rare autosomal recessive disorder; this means that both parents must contribute a defective gene to the child to show symptoms of the disease. It is usually a disease of children but it can also affect adults.¹ CHS was described first by Beguez Cesar in 1943. Later, Chédiak in 1952 described the full clinical and haematological features, and Higashi in 1954 discovered that the inclusions are peroxidase (Sudan Black B) positive. The gene responsible for this defect was characterized in 1996 as the lysosomal trafficking regulator (LYST or CHS1 gene). It is located on chromosome-1 (1q42-43).¹ There are two types of mutations responsible for the disease i.e. frameshift and nonsense. Both are associated with clinically mild and severe form of disease.²

CHS protein is expressed in the cytoplasm of the cells of different tissues like blood (neutrophils, lymphocytes, histiocytes), melanocytes, neurons etc. and may represent an abnormality of organeller protein. It is characterized by recurrent pyogenic infection, partial oculo-cutaneous albinism, mild coagulation defect and progressive peripheral neuropathy.^{3,4} Neurological symptoms manifest in approximately half of the affected individuals. These patients exhibit alteration in neutrophils which include neutropenia, decreased deformability, resulting in impaired chemotaxis; and delay in the fusion of phagolysosomes leading to defective bactericidal activity.²

Although it is an inherited disorder present since birth, mostly the patients present in an accelerated phase (50-85%) with fever, lymphadenopathy, anaemia, hepatosplenomegaly, jaundice, squint and wide spread lymphohistiocytic infiltration.^{2,5} Mortality is high in accelerated phase. Early diagnosis of the syndrome and bone marrow transplantation before the onset of accelerated phase is the only curable treatment.⁶

The present patient presented with Chediak-Higashi syndrome in accelerated phase which has poor prognosis.

CASE REPORT

A 2 years old boy presented to Paediatric Department of Fauji Foundation Hospital, Rawalpindi, with high grade fever, cough, swelling of neck and abdominal distention for the last 15 days. He was treated for these symptoms in a local hospital and afterwards in Fauji Foundation Hospital, Kalar Kahar, from where he was referred to Fauji Foundation Hospital (FFH), Rawalpindi, because of his deteriorating condition.

The patient had previous history of similar episodes but with lesser intensity. On physical examination, he had pallor, hepatosplenomegaly significant cervical lymphadenopathy, swollen tonsils covered with whitish membrane and enlarged axillary and inguinal lymph nodes. He also had silver hair and partial cutaneous albinism since birth (Figure 1). One of his siblings had died at the age of 3 years with similar physical appearance (silver hair and albinism) and clinical symptoms including splenomegaly for which he did not get proper medical treatment. Two other siblings were healthy. His parents were first cousins. Due to his serious illness, he was put on inj. co-amoxiclav 50 mg/kg TDS, inj. dexamethasone 0.5 mg/kg B.D and syrup fluconazole TDS. His routine investigations were carried out, complete blood picture showed W.B.C count of $5.3 \times 10^9/L$, Hb level of 9.2 gm/dl, Hct of 30%, platelet count

¹ Department of Haematology / Pathology² / Paediatrics³, Fauji Foundation Hospital, Rawalpindi.

⁴ Department of Pathology, Foundation University Medical College, Rawalpindi.

Correspondence: Dr. Tanzeel Imran, Department of Haematology, Fauji Foundation Hospital, Jehlum Road, Rawalpindi.

E-mail: dr_tanzeel@yahoo.co.uk

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Figure 1: Features of Chediak-Higashi syndrome with silver hair, partial albinism and bilateral cervical lymphadenopathy.

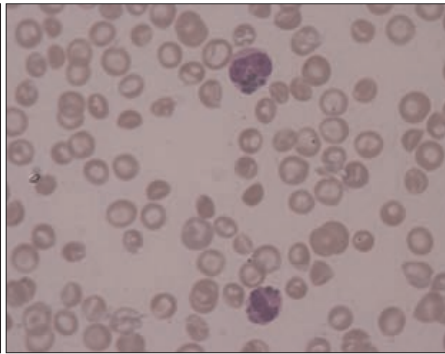


Figure 2: Peripheral blood film showing large inclusions within neutrophils.

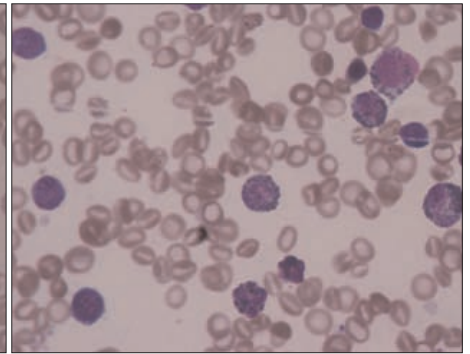


Figure 3: Bone marrow aspirate showing large inclusions within myeloid precursors.

of $113 \times 10^9/L$, MCV of 70 fl, differential leucocyte count showed neutrophils 47%, lymphocytes 41% and monocytes at 11%. Coagulation studies revealed PT of 16/second and APTT 34/second. His serum total bilirubin was 70 $\mu\text{mol/L}$, ALT was 79U/L, ALP 1910 U/L and serology was negative for HBV/HCV.

In view of his clinical presentation and bicytopenia, he was referred for bone marrow aspiration to rule out leukemia/lymphoma. Examination of his peripheral blood film showed large gray green inclusions in almost all granulocytes and lymphocytes (Figure 2). These inclusions were also appreciated on bone marrow aspirate (Figure 3) and were Sudan Black B positive. Bone marrow aspirate also revealed prominent histiocytes and haemophagocytosis. On the basis of his clinical presentation, peripheral blood film and bone marrow aspirate findings, the diagnosis of Chediak-Higashi syndrome was established. Bone marrow trephine was consistent with aspiration findings.

As he had enlarged cervical lymph node, fine needle aspiration cytology was done that showed reactive lymphadenitis. Examination of the eyes revealed decreased iris pigmentation. Molecular studies were not carried out because of unavailability. The patient's condition kept on deteriorating with the development of diarrhea and fits although his cerebrospinal fluid (CSF) routine examination and culture sensitivity, metabolic profile and renal functional test were normal. His treatment was changed to Inj. imipenam 60 mg/kg TDS, Inj. amoxicillin 20 mg/kg/day in 4 divided doses and syrup cotrimoxazole 50 ml B.D. The patient received multiple transfusions including platelets, packed red blood cells and fresh frozen plasma because of severe bleeding. Unfortunately patient expired after 24 days of hospital stay.

DISCUSSION

Chediak-Higashi syndrome is a rare autosomal recessive disorder that affects multiple systems of the body.¹ Two cases have been reported from Pakistan. Ahmed and his colleagues reported a 13 months female baby with fever, pallor, abdominal distention, recurrent

infections and cutaneous albinism.³ Her brother died with similar complaints at the age of 11 months and her parents had consanguineous marriage.

Children are more commonly affected though it can also occur in adults.¹ The average life span of children affected by this disease is 6 years. The disease has two phases, chronic (stable) and accelerated (progressive). The chronic phase is characterized by repeated infections. The first accelerated phase of this disease may occur shortly after birth or may occur in affected individual many years later.⁷ Long surviving patients may develop rare complications of olivo-cerebellar degeneration and amyloid deposits.^{6,8}

Recurrent bacterial skin infections with *S. aureus* and *Streptococcus* spp. are seen in the chronic stable phase of this disease. Therefore, adequate hygiene should be maintained to avoid recurrent bacterial infections.⁷ The skin should be washed with disinfectant soap to prevent skin infections. Fingernails should be kept at short length to reduce autoinoculation.

Genetic defects of platelets give rise to bleeding disorders of varying severity. Spontaneous bleeding is mostly muco-cutaneous and of mild to moderate severity. In accelerated phase transfusion of platelets remains the most common treatment while in mild bleeding, management with desmopressin is recommended. Drugs that interfere with platelet function (e.g. acetylsalicylic acid containing products) should not be used.⁴ This patient also had bleeding from nose, gums and finally intracranial bleed leading to death.

Epstein-Barr virus (EBV) is implicated in the accelerated phase. It is thought that the inability to clear the EBV infection leads to a state of constant lymphoproliferation resulting in leukemia/lymphoma like picture as seen in the accelerated phase of disease.⁹ Nargund and colleagues have reported a case that was referred to them with bilateral neck swellings and the clinical diagnosis of leukemia/lymphoma.⁷ This patient had a similar presentation and was referred to us for suspicion of leukemia/lymphoma.

Chediak-Higashi syndrome (CHS) is one of the causes of Haemophagocytic Syndrome (HPS).¹⁰ Epstein-Barr

virus may be responsible for the haemophagocytic syndrome caused by CHS. Phagocytosis of blood cells and their precursors is a hallmark of haemophagocytic syndrome.^{9,10} Activated macrophages may engulf erythrocytes, leukocytes, and platelets, their precursors, and cellular fragments causing cells to appear filled-up with other blood cells. Prominent haemophagocytosis is seen in bone marrow, spleen, lymph nodes, skin and central nervous system. Haemophagocytosis may also be present in the liver.¹⁰ These features were also seen in our patient in bone marrow aspirate and trephine biopsy.

Prognosis of CHS is generally not favourable especially once the accelerated phase has started; the syndrome is usually fatal within 30 months of onset of accelerated phase. Usual cause of death is infection and bleeding. Allogeneic bone marrow transplant is the treatment of choice.⁶ Accelerated phase should be treated with appropriate antibiotics, antiviral, ascorbic acid, blood component transfusion and GM-CSF injections to achieve remission.^{5,7} The favourable outcome in this phase after transplant is achieved only if it is performed when patient is in remission.⁶ This patient presented late and in accelerated phase, so mainstay of treatment was supportive care. Tardieu *et al.* studied the clinical course of 3 patients who underwent successful allogeneic bone marrow transplant with no recurrence of infection or haemophagocytic syndrome.⁸ However, these patients developed neurologic deficit manifested by difficulty in walking, loss of balance, and tremor later on during their adult life.⁸

The differential diagnosis of CHS includes Griscelli and Elejalde syndromes.¹¹ These are all autosomal recessive syndromes. Elejalde syndrome is differentiated from the other two syndromes by the facts that it does not enter into the accelerated phase and recurrent infections and immune defects are not manifested in it. Giant leukocytic granules are the only major differentiating point between

Griscelli and Chediak-Higashi syndrome as seen only in Chediak-Higashi syndrome.

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