

Accelerated Phase of Chediak Higashi Syndrome: An Unusual Case of Pancytopenia

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Keywords: Accelerated Phase, Bone Marrow, Chediak Higashi, Leukocytes, Pancytopenia.

ABSTRACT

Chediak Higashi Syndrome (CHS) is a rare and fatal disease with varied clinical features and laboratory findings. Early diagnosis can be made by screening the blood smear and bone marrow for giant granules in leukocytes. Accelerated phase has poor prognosis. Hematopoietic stem cell transplantation (HSCT) has good role, if done in early stage of disease. Hence, a prompt and accurate diagnosis should be given, so that timely intervention can be done. The present case highlights an accelerated phase of CHS in an infant presenting for the first time with recurrent infections and organomegaly.

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Introduction

Chediak Higashi Syndrome (CHS) is a rare autosomal recessive and fatal congenital disorder characterized by blonde hair, recurrent infections, ocular abnormalities, bleeding diathesis and neurological impairment along with abnormally large granules in leukocytes. Accelerated phase of the disease has poor prognosis and is infrequent to notice this phase at initial presentation [1]. Diagnosis is made on the basis of clinical features, hair analysis and identification of characteristic giant azurophilic granules in white blood cells in peripheral smear and bone marrow aspirate/ biopsy. Herein, we present a case of an infant with CHS presenting in accelerated phase.

Case Report:

A 1 year old male child presented with complaints of fever for one and a half months, abdominal distension for 10 days and bleeding from ear for 2 days. He also had a history of repeated episodes of loose stools for last six months and one episode of melaena. History of febrile illness at 9 and 11 month of age was also given by the parents, nature of which was not known. The child was product of non-consanguineous marriage (single child from second marriage). The mother's first husband died due to brain tumor (she had three children from the first marriage- one alive 11 year old female child, the other two siblings died; however, the cause of death was not known). The patient also had history of tuberculosis contact. On examination, child had pallor, silver-grey hair, hypopigmentation in iris and also over face, trunk, abdomen and limbs along with massive hepatosplenomegaly (Fig 1-2).

Blood examination showed pancytopenia with hemoglobin-8.9gm/dl, total leukocyte count -2200/ μ L and platelet count-30,000/ μ L (Fig 3). Red blood cells showed mild to moderate anisopoikilocytosis with predominantly microcytic hypochromic picture. Neutrophils showed presence of coarse, large eosinophilic granules (Fig 4, 5 B). Coarse granules were also seen in lymphocytes & some monocytes (Fig 3, 5 A). Bone marrow examination revealed maturing cells of myeloid series with presence of coarse large round, eosinophilic granules. An evidence of hemophagocytosis was also noted.

Ultrasound of the abdomen revealed hepatosplenomegaly. Biochemical investigations showed increased levels of serum triglycerides and serum ferritin. Histological examination of hair shafts showed evenly distributed melanin granules of regular diameter that were bigger than those seen in normal hair. On the basis of clinical details along with biochemical, hematological and radiological findings, a diagnosis of "Accelerated phase of Chediak Higashi syndrome" was made.



Fig. 1: Child with abdominal distension and hypopigmented areas (red arrow).



Fig. 2 A & B: Child presented with silvery grey hair.

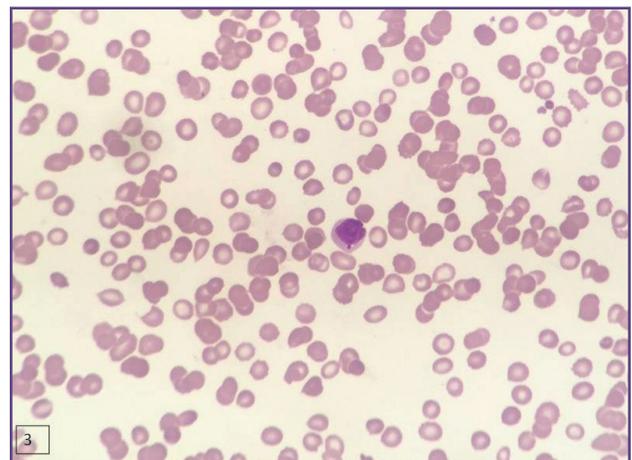


Fig. 3: Peripheral smear from child with CHS showing pancytopenia and lymphocyte showing granule in cytoplasm (Giemsa X100).

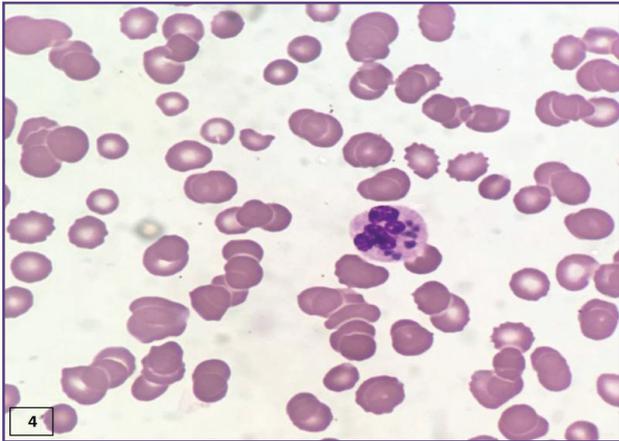


Fig. 4: Neutrophil showing giant granules in cytoplasm (Giemsa X200).

Discussion

Chediak Higashi Syndrome is a rare disorder affecting multiple system of body characterized by partial oculocutaneous albinism, severe immune deficiency resulting in recurrent infections, pathognomonic abnormal giant granules in neutrophils, lymphocytes, monocytes, platelets and an accelerated lymphohistiocytic phase. It is an autosomal recessive disease, both parents contributing a defective gene to the child to show symptoms. This disorder is seen in children but rare cases have been reported in adults [2].

This disease entity was first described by Beguez Cesar in 1943, in three siblings presenting with neutropenia and abnormal granules in leukocytes [3]. In 1952, Chediak (Cuban hematologist), described the full clinical and hematological features and in 1954, Higashi (Japanese pediatrician) discovered the Sudan block B (SBB) positivity for inclusion [3,4].

The age of onset is usually 4-10 years, mean age being 6 years and most of the children die before age of 10. Even if child is alive, he/she will develop neurological problems [5]. This disease is described in 2 phases, i.e. chronic (stable) and accelerated (progressive). In stable patients, there is history of repeated infection. Accelerated phase of this disease can occur shortly after birth or may occur years later. In children, who develop accelerated phase, later in life, complication like olivo-cerebellar degeneration and amyloid deposits may also occur [5].

In the case presented here, the child was just one year old and presented in accelerated phase of the disease, however, no neurological impairment was noted in the child. The patient presenting in chronic phase present with recurrent bacterial skin infection with *Staphylococcus*

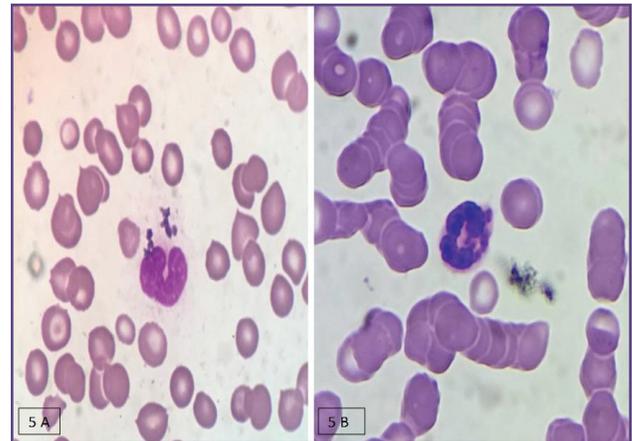


Fig. 5 A & B: Granules in WBCs (monocyte & neutrophil) in Peripheral smear from child with Chediak Higashi Syndrome (Giemsa X400).

aureus and *Streptococcus* species. Strict hygiene should be maintained to prevent any further infection. Platelet transfusion is given for treatment in accelerated phase, if the patient presents with bleeding episodes. Hence, drugs interfering with platelet function should be avoided. The child in present case had an episode of melaena before being admitted to hospital.

Role of Epstein Barr Virus is also implicated in the accelerated phase, causing persistent lymphoproliferation resulting in leukemia/ lymphoma, just like in accelerated phase of disease [6]. As the presentation of the patients with CHS is vague and non-specific, clinically, sometimes, there can be confusion with leukemia/ lymphoma. Nargund et al reported a similar case of CHS, where the initial clinical diagnosis given was leukemia/ lymphoma [6]. Hemophagocytic syndrome (HPS) is an important consideration to be kept in mind while assessing CHS.

The accelerated phase is seen in 85% of individuals affected with CHS [7]. The diagnosis of accelerated phase is done according to the guidelines of Histiocytic Society last revised latest in 2004 [7]. This is based on the presence of a genetic defect like mutation in *LYST* gene done by sequence analysis or five of the following 8 features:

1. History of unexplained, persistent or recurrent fever
2. Splenomegaly
3. Cytopenias (in any 2 of lineage)
4. Hypertriglyceridemia and/ hypofibrinogenemia
5. Evidence of hemophagocytosis in bone marrow
6. Low or absent NK cell activity
7. Elevated serum ferritin levels (>500 microgram/L)
8. Elevated CD25 levels (> 2400 U/ mL)

In the present case, diagnosis of accelerated phase of CHS was given as the patient presented with persistent fever, diarrhoea, ear bleed, discolouration of face, trunk, abdomen, limbs, blonde hair, hypopigmentation of eyes, increased serum ferritin levels, hypertriglyceridemia and hepatosplenomegaly with characteristic peripheral smear and bone marrow findings.

In CHS, the characteristic feature is presence of huge lysosomes and cytoplasmic inclusions within different hematopoietic cells like WBCs. Molecular defect seen is the abnormality in granule morphogenesis which is due to mutation of lysosomal trafficking gene 2, termed as CHS1/LYST gene and located on long arm of chromosome 1 (1q). This results in abnormality in function of lysosomal trafficking regulator protein and ultimately affecting the size and function of lysosomes. Accelerated phase of CHS has usually an unfavorable prognosis resulting in fatal outcome. The causes of death are usually infection and bleeding. Ideally, allogeneic bone marrow transplantation is the treatment of choice for patient diagnosed early with CHS, especially in chronic phase or if the patient is in remission [11]. Results are not effective in accelerated phase of the disease. Treatment given is supportive management with appropriate antibiotic, antiviral therapy, ascorbic acid and management of complications with platelet transfusion. Some trials for etoposide, steroid, intrathecal methotrexate have also been done [7]. Parental screening for this disease is also important using blood smear. Prenatal screening can be done by showing lysosomal phosphatase positivity in amniocytes, chorionic villous sampling [8].

Giant granules can also be noted in AML/ CML and are termed as Pseudo-CHS anomaly [7, 8]. The other diseases which show few of the similar features as CHS are Prader Willi and Angelman, presenting with hypopigmentation but no ophthalmic albinism. However, few of the genetic disorders show oculocutaneous albinism like Griscelli syndrome & Hermansky-Pudlak syndrome, but in both these diseases no giant granules are noted. Considering the clinical, peripheral blood and bone marrow cytomorphological findings, few differential diagnoses which can be considered in the present case have been tabulated below (Table 1) [7, 8].

In the present case, the child had recurrent infections and giant leukocytic granules in peripheral smear and bone marrow aspirate, which helped in differentiating CHS from the other diseases as mentioned above (Table No.1). Based on the clinical, biochemical, hematological and radiological investigations, a diagnosis of accelerated phase of CHS was made. As stem cell transplantation is the definitive treatment for this case, child was given supportive management and advised for marrow transplantation.

Table 1 Differential diagnosis for Chediak Higashi Syndrome

	Chediak Higashi Syndrome	Elejalde disease	Griscelli disease
Mode of inheritance	Autosomal recessive (AR)	AR	AR
Recurrent infection & immune defect	Present	Absent	Present
Accelerated phase	Present	Absent	Present
Giant leukocytic granules	Present	Absent	Absent

Conclusion

Chediak Higashi Syndrome is a rare inherited hematological disorder of neutrophil function defect in paediatric age group. The presence of characteristic clinical profile and characteristic cytomorphological findings in peripheral smear and bone marrow aspirate smears is important for the diagnosis of CHS in the accelerated phase. As it is an autosomal recessive condition screening the family members can help detect the disease. Molecular testing for CHS1 gene, if available, is helpful for prenatal diagnosis in suspected cases. Hematopoietic Stem Cell Transplantation (HSCT) is the only curative treatment. Early stem cell transplant offers better survival and cure.

Acknowledgements

None

Funding

None

Competing Interests

None Declared

Reference

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