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CASE REPORT

Accelerated phase of Chediak-Higashi syndrome-a case report with review of literature

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Abstract:

The Chediak Higashi Syndrome (CHS) is a rare autosomal recessive disease characterized by partial oculo-cutaneous albinism, frequent pyogenic infections, presence of giant granules in leucocytes and other granule containing cells. Associated findings include silvery hair, photophobia, horizontal and rotatory nystagmus, hepatosplenomegaly and peripheral neuropathy. Mutation of the LYST gene defines the syndrome. The first case of Chediak Higashi Syndrome was reported in 1943. Since its first description, around 170 cases have been reported in the literature till date and 10 cases have been reported from India.

Keywords Chediak-Higashi, accelerated phase, abnormal granules

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Introduction

Chediak Higashi Syndrome (CHS) is an autosomal-recessive disorder characterized by partial ocular and cutaneous albinism, increased susceptibility to pyogenic infections, the presence of large lysosome-like organelles in most granule-containing cells, and a bleeding tendency. The abnormal granules are most readily seen in blood and marrow leukocytes, especially granulocytes and in melanocytes [1,2]. Giant granules may also be present in lymphocytes, monocytes, platelets, renal tubular cells, pneumocytes, gastric cells, hepatocytes, neuronal cells and fibroblasts [3]. Many patients later develop an accelerated phase characterized by fever, lymphadenopathy, anemia, jaundice, neutropenia, thrombocytopenia, and widespread lymphohistiocytic organ infiltrates [1].

Case Study

A 7 year old male child born of second degree consanguineous marriage presented with fever, cough and loss of appetite since 10 days with history of epistaxis and malaena since 2 days. There was a history of difficulty in standing and walking since the last 5 years. At presentation, the child could walk only with support.

There was history of repeated hospitalisation in the last four years, the commonest cause being lower respiratory infections, followed by gastrointestinal infections and one episode of encephalitis. On examination, the child was anthropometrically below normal for age, irritable, febrile and pale. There was bilateral pitting pedal edema, hepatomegaly and splenomegaly with Grade 3 power in both lower limbs. The child had a silvery gray metallic sheen of the hair with hypopigmentation of the skin over the forehead and irregular patches of skin devoid of pigment at multiple sites all over the body. Ophthalmic consultation revealed presence of nystagmus, photophobia and bilateral large discs with severe chorio-retinal degeneration. Laboratory examination revealed a Hb of 7.3g%, TC – 25,098cells/mm³, N-31, L-60, E-04, M-05, ESR – 15mm at the end of 1 hour and Platelets – 45,000/mm³. Peripheral smear examination showed abnormally large granules in the neutrophils, lymphocytes and monocytes as well (Figures 1a, 1b, 1c). Majority of the granulocytes showed 1-3 granules with few of them showing multiple granules. An interesting finding was that these abnormal granules remained intact even within smudge or basket cells (Figure 1d, 1e). Chest X-ray showed bilateral bronchopneumonia. Based on the clinical

presentation and haematological findings, a diagnosis of accelerated phase of Chediak Higashi Syndrome was made.

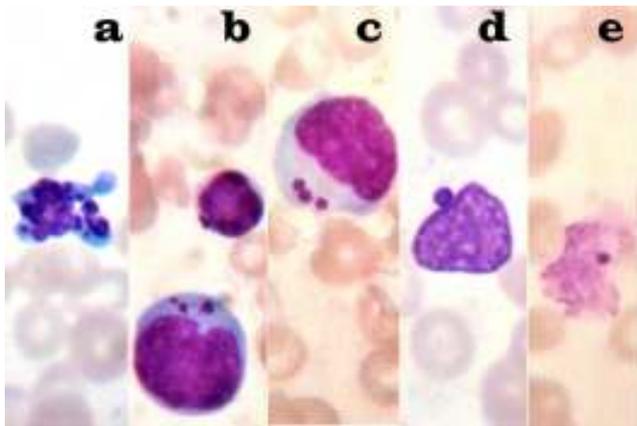


Figure 1a,1b,1c: Peripheral Smear depicting abnormal granules in the neutrophils, lymphocytes and monocytes respectively. Figure 1d,1e: Abnormal granules in the smudge cells.

Discussion

CHS was first described by Bequez-cesar in 1943. Later Chediak, a Cuban hematologist and Higashi, a Japanese paediatrician described a series of cases in 1952 and 1954 respectively. In 1955 Sato coined the term Chediak-Higashi syndrome [4].

In 2000, a study conducted in CHS patients from multiple families revealed mutations in the lysosomal trafficking regulator (LYST) gene on chromosome 1. CHS has been listed in OMIM bearing the number #214500 [5].

The pathognomonic cytoplasmic granules of CHS can be seen in all the granulocyte series. In our case, majority of the granulocytes showed either single or two granules with occasional cells showing multiple granules. These granules are peroxidase positive. In neutrophils, these anomalously large, granules have been shown by electron microscopy to be abnormal primary (azurophilic) granules. In lymphocytes and plasma cells, they may be primary granules. The abnormal granules in monocytes result from granule fusion and may be phagolysosomes [1,6].

Patients with this syndrome exhibit an increased susceptibility to infection, which can be explained partly due to defects in neutrophil chemotaxis, degranulation, and bactericidal activity [1].

Neurological manifestations occur in approximately half of the patients. The neuropathy may be sensory or motor in type, and ataxia may be a prominent feature. The mechanism of peripheral neuropathy in Chediak-Higashi

syndrome has not been completely elucidated. Both the axonal type and the demyelinating type of peripheral neuropathy have been reported [7].

About 50-85% of the patients with CHS enter into an accelerated phase manifested by fever, anemia, jaundice, neutropenia, thrombocytopenia, hepatosplenomegaly and lymphadenopathy. This accelerated phase is the most life threatening clinical feature of CHS, as was seen in our case. The accelerated phase may occur shortly after birth or several years later, which may be fatal if left untreated [7]. The child was treated with antipyretics, antibiotics and ascorbic acid. The child's condition improved after a week and was discharged. HSC (Haematopoietic Stem Cell) transplantation was recommended. In a study conducted by Eapen et al, the outcome after HSC transplant in 35 patients with CHS was studied. Death rate and recurrence rate was high in those patients in whom transplantation was performed during the accelerated phase. Hence it was concluded that transplantation done in remission after the accelerated phase may improve the disease free survival [8].

Differential diagnosis of CHS includes Griscelli syndrome, Hermansky Pudlak syndrome and Elejalde syndrome. However, in all these oculocutaneous albinism syndromes the characteristic giant granules in neutrophils which are the hallmark of CHS is lacking [9]. Acute and chronic myeloid leukemia may show giant granules resembling those seen in CHS, also referred to as pseudo-Chediak Higashi anomaly [10].

Whenever a child presents to the hospital with oculocutaneous albinism and recurrent infections, CHS has to be the most important differential diagnosis which can be diagnosed by doing a careful examination of the peripheral blood smear by an experienced morphologist. Early diagnosis facilitates early HSC transplantation, which is the only possible cure.

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