## Case Report

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# Chediak Higashi syndrome presenting in accelerated phase: a case report and literature review

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#### **ABSTRACT**

Chediak Higashi syndrome (CHS) is a rare autosomal recessive lysosomal disorder characterized by frequent infections, oculocutaneous albinism, bleeding diathesis and progressive neurologic deterioration. In 85% of cases, CHS patients develop the accelerated phase characterized by pancytopenia, high fever, and lymphohistiocytic infiltration of liver, spleen, and lymph nodes. Treatment of accelerated-phase CHS is difficult and the prognosis is poor. Here, we report a case of CHS in a 1-year-old girl who presented in the accelerated phase of the disease. CHS diagnosis was made on the basis of clinical characteristics, hair analysis and identification of pathognomonic giant azurophilic granules in peripheral blood smear.

Keywords: Accelerated phase, Chediak Higashi syndrome, Hematology, Treatment

### INTRODUCTION

Chediak Higashi syndrome (CHS) is a rare autosomal recessive disorder with fewer than 500 cases published worldwide over the last 20 years. The clinical features of this syndrome include partial albinism, photosensitivity, severe recurrent bacterial infections, bleeding diathesis and late onset neurological manifestations (central and peripheral neuropathies, sensory loss, muscle weakness, parkinsonism, cerebellar ataxia, and cognitive impairment). Approximately 85% of cases develop a fatal accelerated phase characterized by pancytopenia, hemophagocytosis, and marked infiltration of organs by lymphocytes, leading to multi-organ dysfunction.

Owing to the rarity of the condition and the characteristic clinical and hematological findings, we report a case of Chediak Higashi syndrome, which presented in accelerated phase.

### **CASE REPORT**

A 11 month old female infant, second born to non consanguinously married couple with normal birth history, significant past history of repeated hospitalisation for respiratory tract infections, incompletely immunised as per NIS, developed appropriate as per age was brought with complaints of fever since 16 days, Swelling behind ear since 14 days, cough since 6 days, Abdominal distension since 6 days.

On general examination child had significant pallor, mild abnormal facies, generalised lymphadenopathy, hypopigmented skin, hair and abdominal distension. Systemic examination showed Massive Splenohepatomegaly (Figure 2).

Routine investigations done showed Anemia with Thrombocytopenia.

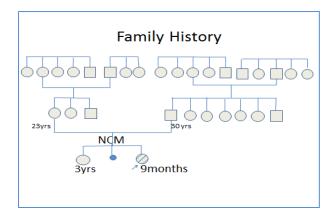


Figure 1: Family pedigree chart.



Figure 2: Hypopigmented skin and silvery hair.

Peripheral smear showed normocytic hypochromic anemia with thrombocytopenia and lymphocytosis and typical Chediak Hegashi granules (Figure 3). Microscopic examination of hair shaft showed decreased pigment granules (Figure 4). Both parents were evaluated and found to be carriers of Chediak Hegashi syndrome and Chediak Hegashi granules were seen on the Peripheral smear. Elder sibling was also evaluated and peripheral smear was found to be normal.



Figure 3: Peripheral smear showing typical Chediak Hegashi granules.

Child was started on symptomatic treatment. She developed respiratory distress and continuous nasogastric bleed 5 days after admission, and inspite of all resuscitative efforts child succumbed to death.

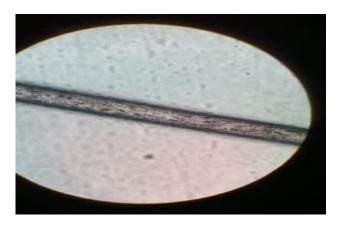


Figure 4: Microscopic examination of hair follicle showing decreased pigment granules.

#### **DISCUSSION**

CHS was first described over 60 years ago by Beguez-Cesar in three siblings bearing the main clinical features of neutropenia and abnormal granules in leukocytes.<sup>5</sup> Chediak, a Cuban hematologist, reported another case in Higashi, a Japanese pediatrician, described a series of cases finding misdistribution of myeloperoxidase in the neutrophilic granules of affected patients.<sup>6,7</sup> CHS is a rare disease (approximately 500 cases reported worldwide), the prevalence and incidence of which are unknown. In a nationwide survey in Japan, 15 patients were diagnosed during a period of 11 years (2000–2010), indicating that one or two patients with CHS were diagnosed each year.<sup>8</sup>

The mean age of onset is 5.85 years; however, most patients die before age 10. In patients that do survive beyond childhood, neurological problems persist and/or increase in magnitude.<sup>9</sup>

In an Indian study of five children with CHS, accelerated phase was seen in three cases, with all three resulting in fatal outcomes.<sup>10</sup>

Clinical and laboratory findings by Farhoudi et al in six cases of CHS reported hypopigmentation of the skin, silvery hair, photophobia, and nystagmus observed in all patients, a history of recurrent infections in four patients, and accelerated-phase progression in three patients.<sup>11</sup>

Roy et al studied the clinico-hematological profile of five cases of CHS, reporting that all patients had silvery hair, partial albinism, photophobia, and recurrent skin and/or chest infection, with three of them (50%) presenting an accelerated phase.<sup>12</sup>

Of the 15 patients enrolled in the Japanese study, 10 (67%) had recurrent bacterial infections, five (33%)

developed life-threatening HLH, and one patient had complicated malignant lymphoma.<sup>8</sup>

CHS is characterized by partial oculocutaneous albinism, repeated infections, and pathognomonic abnormal giant granules in neutrophils, lymphocytes, monocytes, and platelets. Patients develop recurrent infections that most commonly involve the skin and respiratory system. *Staphylococcus aureus* and beta-hemolytic *Streptococcus* are the predominant organisms. Viral and fungal infections, however, have also been described <sup>13</sup>. Increased susceptibility to recurrent infections is attributed to defects in T-cell cytotoxicity and natural killer function and defects in granulocyte chemotaxis and bactericidal activity. <sup>13</sup>

The accelerated phase is observed in 85% of individuals and can occur at any age, including shortly after birth or within several years. Clinical manifestations include fever, lymphadenopathy, hepatosplenomegaly, anemia, neutropenia, thrombocytopenia, and neurological abnormalities. Originally thought to be a malignancy resembling lymphoma, the accelerated phase is now known to be an HLH characterized by multi-organ inflammation. The accelerated phase and its complications are the most common cause of mortality in individuals with CHS. Prognosis associated with the accelerated phase is poor.

The genetic hallmark of CHS is mutations in the CHS1/LYST gene located on chromosome 1q42-43.14 Mutations of this gene result in a defect in granule morphogenesis in multiple tissues.<sup>6</sup> The gene encodes a protein called the lysosomal trafficking regulator <sup>15</sup> which regulates the synthesis, transport, and fusion of cytoplasmic vesicles. The abnormalities observed in these vesicles result in grossly enlarged and nonfunctional lysosomes, which are identified during cytology as giant coalesced azurophilic granules present mostly in granulocytes and monocytes, but also fibroblasts, melanocytes, astrocytes, Schwann cells. hematopoietic cells. 15 These granules are specific to CHS and their presence in granulocytes from peripheral blood and bone marrow is the basis of diagnosis. 16

Clinical CHS phenotypes correlate with molecular genotypes. CHS patients with deletions in the LYST gene usually present with a fulminant accelerated phase early in life, whereas, those with missense mutations have a better prognosis, characterized by the absence of an accelerated phase and no neurological involvement. <sup>17</sup> Our patient had a rapidly fatal course, thus, genetic analysis has not been undertaken.

The only treatment that cures the hematologic and immunologic defects is allogenic hematopoietic stem cell transplantation (HSCT), but this therapy does not prevent the progressive neurological dysfunction frequently observed during long-term follow up.<sup>1,13</sup>

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