CASE REPORT

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 2-year-old boy 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 and bone marrow.

Chediak Higashi syndrome (CHS) is a rare autosomal recessive disorder with fewer than 500 cases published worldwide over the last 20 years [1]. The largest CHS study to date included 15 patients [2]. In Tunisia, Bouatay et al. (2014) [3] reported a single case of CHS. 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) [4,5]. 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 [6].

Owing to the rarity of the condition and the characteristic clinical and hematological findings, we report a case of Che-diak–Higashi syndrome, which presented as accelerated phase.

Case report

The patient is a 2-year-old male that presented with a month-long history of fever, abdominal distension, and cough. There was a prior history of repeated attacks of low respiratory-tract infections and he developed osteomyelitis at 1 year of age. He is the third child from a consanguineous marriage, displays normal psychomotor development, and there is no family history of the disease. On examination, the patient was febrile, of average build, weighed 14 kg, and had blond hair and hypopigmentation of the skin (Figure 1). The child was anemic, with cervical and axillary lymphadenopathy. Respiratory system examination revealed moderate respiratory distress with bilateral coarse crepitations. The patient had a protuberant abdomen with massive hepatosplenomegaly. The cardiovascular and nervous systems were normal.

Laboratory investigations showed elevated C-reactive protein (132 mg/L), hyponatremia (124 mmol/L), high ferritin levels (2685 ng/mL), low fibrinogen levels (<1.5 g/L), and hypertriglyceridemia (3.57 mmol/L). The relevant hematological findings were hemoglobin 5.2 g/dL, leucopenia at 3.56 \times 10^9/L, and thrombocytopenia (Platelet count 26 \times 10^9/L). Peripheral blood smear showed several abnormal giant granules in most leukocytes. Bone marrow aspirate revealed prominent granules within the lymphocytes and myeloid cells (Figure 2). Phagocytosis of red blood cells and red-blood-cell precursors hemophagocytosis was also observed (Figure 3).

The patient fulfilled the diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH), e.g., prolonged fever, splenomegaly pancytopenia, high ferritin levels, low fibrinogen levels, hypertriglyceridemia, and hemophagocytosis. Thus, the diagnosis of accelerated phase of CHS was

Figure 1  Face of the patient. Note skin hypopigmentation and blond hair.

Figure 2  Bone marrow aspirate (A–C) and peripheral blood (D) smear showing myeloid precursor and lymphocytes with abnormal granules.
made on the basis of clinical presentation (hypopigmentation, blond hair) and hematological findings (giant azurophilic granules in leukocytes).

Blood and urine cultures were negative. Serologies of Epstein–Barr virus, cytomegalovirus, and Aspergillus were negative. Because of recurrent and severe infections, we initiated immune-system investigation. The patient had normal immunoglobulin levels and T and B cells (CD3, CD4, CD8, and CD19) were examined using flow cytometry, however, chemotaxis of natural killer cells was not studied. Optical microscopy examination of the hair showed groups of pigment scattered along the length of the hair shafts, contrasting with the normal pattern of fine, diffuse pigmentation (Figure 4). Chest X-ray showed opacities in interesting bilateral lower zones. Chest computed tomography showed two cavitary lesions of the middle right pulmonary lobe (Figure 5). Abdominal ultrasound revealed hepatosplenomegaly with a normal echo pattern.

The child was treated with ceftazidime, Vancomycin, and fluconazole. He received high doses of intravenous gammaglobulin (1 g/kg per day for 2 days). He also received multiple transfusions, including platelets and packed red blood cells for anemia. He died 7 days after admission because of status epilepticus and multi-organ failure.

**Discussion**

CHS was first described over 60 years ago by Beguez-Cesar (1943) [7] in three siblings bearing the main clinical features of neutropenia and abnormal granules in leukocytes. Chechiak, a Cuban hematologist, reported another case in 1952 [8] and in 1954, Higashi, a Japanese pediatrician, described a series of cases finding misdistribution of myeloperoxidase in the neutrophilic granules of affected patients [9]. 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 [2].

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 [10].
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 [11]. 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 [12].

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 [10]. 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 [11]. Prognosis associated with the accelerated phase is poor. In an Indian study of five children with CHS, accelerated phase was seen in three cases, with all three resulting in fatal outcomes [13].

Clinical and laboratory findings by Farhoudi et al. (2003) [14] 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.

Roy et al. (2011) [13] studied the clinic-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.

Of the 15 patients enrolled in the Japanese study [2], 10 (67%) had recurrent bacterial infections, five (33%) developed life-threatening HLH, and one patient had complicated malignant lymphoma. Our patient had hypopigmented skin, blond hair, a history of recurrent low respiratory tract infections, and had developed osteomyelitis 1 year ago.

The genetic hallmark of CHS is mutations in the CHS1/LYST gene located on chromosome 1q42–43 [15]. Mutations of this gene result in a defect in granule morphogenesis in multiple tissues [4]. The gene encodes a protein called the lysosomal trafficking regulator [16] 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, and hematopoietic cells [16]. These granules are specific to CHS and their presence in granulocytes from peripheral blood and bone marrow is the basis of diagnosis [4].

Clinical CHS phenotypes correlate with molecular genotypes. CHS patients with deletions in the LYST gene usually present with a fulminating 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 [17]. 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 allogeneic hematopoietic stem cell transplantation (HSCT), but this therapy does not prevent the progressive neurological dysfunction frequently observed during long-term follow up [1,11].

A conditioning regimen, described in detail by Haddad et al. (1995) [18], generally includes a combination of etoposide, busulfan, and cyclophosphamide. The current standard of care is HSCT as soon as the diagnosis is confirmed and the accelerated phase has either been ruled out or is in remission. The most favored outcome is achieved when HSCT is performed prior to development of the accelerated phase.

If signs of the accelerated phase are present, hemophagocytosis must be brought into clinical remission before HSCT can be performed. Guidelines for treatment of the accelerated phase, revised in 2004 [19], are the same as those for familial hemophagocytic lymphohistiocytosis. Combination therapy consists of etoposide, dexamethasone, and cyclosporine A. Remission is achieved in 75% of individuals within 8 weeks [20] however, relapses are common and response to treatment declines over time. Once remission occurs, prompt HSCT is recommended.

**Conclusion**

CHS is a rare disease with a varied spectrum of clinical presentation and investigation findings. The prognosis of the accelerated phase is poor. HSCT is the only curative treatment for hematological and immunological disorders. We emphasize the need for early diagnosis on basis of characteristic clinical findings and diagnostic laboratory examinations, which leads to early transplantation before development of the accelerated phase.

**Conflicts of interest**

The authors declare no conflicts of interest.

**References**


