

Chediak-Higashi Syndrome Presented with Recurrent Episodes of Diarrhea: A Case Report

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Abstract

Chediak-Higashi syndrome (CHS) is an inherited primary immunodeficiency with an autosomal recessive pattern which is usually identified by partial albinism and frequent pyogenic infections. Herein, we report the interesting case of childhood onset with the main presentation of chronic diarrhea which was treated with dexamethasone and various antibiotics for a chronic fever.

The patient was given etoposide once a week and intravenous immunoglobulin monthly thereafter, which caused partial shrinkage in the size of the liver and spleen and improved the patient's clinical condition. Since CHS is invariably lethal after entering the accelerated phase and early diagnosis may facilitate bone marrow transplantation as the only curative treatment, careful examination in unusual patients without multiple recurrent infections or diagnosed hemophagocytic lymphohistiocytosis should be considered.

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Introduction

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized clinically by partial albinism and frequent pyogenic infections (1). The presence of abnormally large granules in the leucocytes and other granule-containing cells is a pathognomonic criterion, and

absolute diagnosis is based on the morphology of the peripheral blood and bone marrow containing these enlarged granules. Other features of CHS are neutropenia, thrombocytopenia, nystagmus, photophobia, recurrent fever, and periodontitis (2, 3).

Most patients with CHS eventually enter an accelerated phase after variable periods of recurrent infection, although some rare cases present initially with an accelerated phase which is characterized by high fever, hepatosplenomegaly, anemia, jaundice, and lymphohistiocytic infiltration of the liver, spleen, and lymph nodes (4, 5). The accelerated phase makes the prognosis of the disease very poor, mainly because of associated infections and coagulopathies.

The only lifesaving therapeutic intervention for CHS is an allogenic bone marrow transplantation to correct the immunologic and hematologic manifestations of CHS, although it appears to be efficient only if the bone marrow transplantation is performed prior to the accelerated phase or during remission (4, 6). Herein is described an interesting case of Chediak-Higashi syndrome from 2 years ago which presented with chronic diarrhea.

Case presentation

A male child aged three and a half years, the product of a normal pregnancy born at 37 weeks gestation due to PROM, was referred to Children's Medical Center because of prolonged diarrhea and high fever. The parents were first cousins and the patient had no other siblings. The child was found to have silver-blond hair with multiple hypopigmented areas on his face, forehead, and trunk (**Figure 1**). He had no clinical problem during his first year of life, but at one year of age, following the appearance of multiple infected papules on his buttocks and continuing perianal abscess, he was admitted for abscess drainage.

Afterwards, he was frequently admitted due to multiple episodes of diarrhea, fever, upper respiratory tract infection, and once for pneumonia. At 20 months of age, the child underwent adenectomy for tonsillar hypertrophy and congestion. Four months prior to his admission to Children's Medical Center, he had been admitted to another hospital with an enlarged painless right post-auricular and submandibular mass, abdominal distention, diarrhea, and fever; at that time, he was found to have pancytopenia, elevated liver function tests, and lipid profiles. The patient had been diagnosed with Hemophagocytic Lymphohistiocytosis (HLH) and underwent immunochemotherapy on the HLH-94 protocol. The child received high-dose dexamethasone, etoposide (VP16) every week and intravenous immunoglobulin (IVIG) for four months. His condition improved until he was admitted to our center with high fever, poor feeding, and diarrhea. On examination, the child was fair skinned with silver blonde hair, but no ocular albinism was noted. He had bilateral neck swelling with a prominent enlarged right post-auricular and submandibular mass. Hepatomegaly (5 cm below the right subcostal margin) and splenomegaly (6 cm below the left subcostal margin) were noted. The cardiovascular, respiratory, and nervous systems as well as chest X-ray were found to be normal. With these clinical findings, lymphoma was suggested for the patient.

Hematological laboratory findings revealed leucopenia (WBC of 3.0×10^9 /liter, with a differential count of 89% neutrophils, 10% lymphocytes, and 1% monocytes), anemia (hemoglobin 6.3 gr/dL), and

thrombocytopenia (platelet count 28×10^9 /liter). Liver function tests showed increased levels of total bilirubin (17.4 mg/dL), direct bilirubin (9.9mg/dL), aspartate transaminase (AST, 181 U/liter), alanine transaminase (ALT, 182 U/liter). His triglycerides (281 mg/dl), cholesterol (150 mg/dl), and fibrinogen (70 mg/dl) were evaluated. An abdominal CT scan and ultrasound examination showed hepatosplenomegaly and multiple para-aortic lymphadenopathies. The direct smear stool examination reported many cryptosporidium oocysts. The post-auricular mass was found to be an enlarged lymph node which was resected, and its biopsy showed partially affected architecture by proliferated lymphoid cells. The bone marrow aspiration smear was hypercellular with megakaryocytic erythropoiesis. The myeloid series, especially monocytes and myelocytes, showed

single to multiple eosinophilic inclusion bodies surrounded by a clear halo, representing intracytoplasmic giant granules. A peripheral blood smear showed giant granulation of neutrophils and granulocytes (**Figure 2**). Direct microscopy of the patient`s hair revealed an atypical granular distribution of pigmented clumps in his hair shafts (**Figure 3**). Based on these clinical presentations, hematologic and pathologic findings, the patient was diagnosed with the accelerated phase of CHS.

The child was treated with dexamethasone and various antibiotics for the fever. He was given VP16 once a week and IVIG monthly thereafter, which caused partial shrinkage in the size of the liver and spleen and improved the patient`s clinical condition. Since there was no appropriate allogenic candidate, bone marrow transplantation was not performed.

Figure 1. The child was found to have silver-blond hair with multiple hypo-pigmented areas on his face, forehead, and trunk.



Figure 2. Neutrophil with large granules 2, 1000X, o

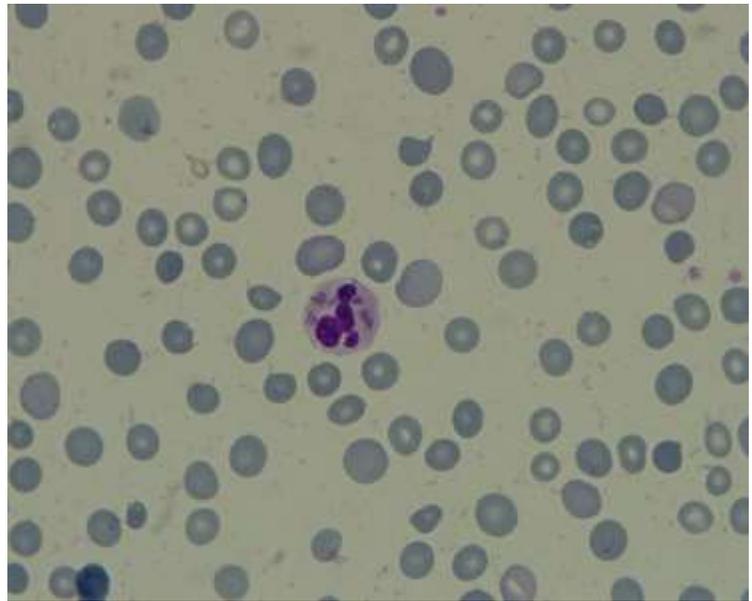


Figure 3. Direct microscopy of patient's hair revealed the atypical granular distribution of pigmented clumps in the hair shaft.



Discussion

Chediak-Higashi Syndrome (CHS) is a rare autosomal recessive disorder typically affecting patients during infancy and early childhood characterized by various findings including partial

oculocutaneous albinism, prolonged bleeding times, recurrent pyogenic infections, abnormal large granules in leukocytes and other granule containing cells, impaired natural killer cell function, and

peripheral neuropathy (7). Patients are often the result of a consanguineous marriage (8-10), as in the present case, but may be from unrelated parents (11).

CHS was first described by Beguez-Cesar in 1943 (12). In 1952, Chediak described the full clinical and hematological features in four members of a Cuban family (13), all children, who showed similar presentations, including pale hair, photophobia, lymphadenopathy and frequent infection, and they died in an early stage of life. Enlarged inclusion like cytoplasmic granules was seen in the granulocytes of the peripheral blood smear and bone marrow of these patients (14). In 1954, Higashi showed that these granules are peroxidase positive and contain lysosomal enzymes (15).

The product of the gene responsible for the defect, named in 1996 as the *CHSI/LYST* gene located on the 1q42 chromosome, is a vesicle trafficking regulatory protein. An imperfection in this protein leads to the aberrant fusion of vesicles and the failure to transport lysosomes to the appropriate site of action (16). This will cause the formation of mega-granules in all types of cells in CHS patients, including abnormally large granules in leukocytes and other granule containing cells like melanocytes, platelets, neural cells, renal tubular cells, and fibroblasts (1, 17). Enlarged granules are usually found in all granule-containing cells in Chediak-Higashi syndrome, whereas in pseudo-Chediak-Higashi syndrome, the granules are only seen in granulocyte lineage cells. The effect of this abnormality is different in different types of cells depending on the function of the granules (18). For

example, an irregular distribution of melanosomes in the hair follicles leads to small aggregates of clumped pigmentation which cause the grayish-silver appearance of a CHS patient's hair. Patients with CHS exhibit alterations in the number and function of neutrophils, including neutropenia, impaired chemotaxis, and phagolysosomal fusion, resulting in recurrent bacterial infections in early stages of life.⁶ Pyogenic infections occur frequently in patients with CHS and can be severe and life threatening. The most common sites of infection are the skin, mucous membranes, lungs, and respiratory tract, and the common organisms involved are usually *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Pneumococcus* species. Cutaneous infections range from superficial pyoderma to deep abscess and ulcerations as seen in our patient.

Only a few patients survive severe infections in early childhood to reach their teenage life. About 50-80% of patients enter into an "accelerated phase" manifested by fever, jaundice, hepatosplenomegaly, lymphadenopathy, and widespread lymphohistiocytic infiltrations in virtually all organ systems with hemophagocytosis, leading to pancytopenia, hypertriglyceridemia, and bleeding disorders secondary to low platelet and fibrinogen levels.^{1, 2} This accelerated lymphoma-like phase is thought to be related to viral infections, particularly the Epstein-Barr virus, and may occur shortly after birth or even several years later; it invariably leads to death if untreated. Treatment with high dose glucocorticoids combined with etoposide (VP16), intrathecal methotrexate, and splenectomy may result in transient remission in the

accelerated phase, but subsequent relapses have been noted to cause the patient to become less responsive to treatment (4, 6).

In approximately half of all CHS patients, neurological manifestations appear in lymphoproliferative lymphoma-like phases such as seizures, mental retardation, and long tract signs. Those patients who survive the infections usually develop a progressive sensory muscular peripheral neuropathy which leads them to become wheelchair bound in their young adulthood. Probably due to an early detection, our case did not show neurological changes. The patient was born with pale silvery-hair but normal eyes and no photosensitivity. He had no clinical problems until one year of age, when he was first admitted with subcutaneous abscess, recurrent fever, and diarrhea. Diarrhea was the common clinical presentation of our patient for more than two years and recurrently happened in association with a high-grade fever. The probability of CHS was first considered when the patient presented with lymphadenopathy, jaundice, fever, and hepatosplenomegaly resembling the accelerated phase of CHS. The presence of abnormal large granules in the granulocytes and lymphocytes of the patient's peripheral blood smear was the first diagnostic evidence which confirmed the diagnosis by direct microscopy of the hair and findings of giant melanosomes in the hair follicles.

The treatment options available for CHS patients are controversial. Parental vitamin C administered in the stable phase of CHS is believed to rule in normalizing neutrophil bactericidal activity, but it has little therapeutic effect during the accelerated

phase. Symptomatic treatment includes antibiotic therapy for acute bacterial infections and blood product replacement for bleeding complications. Allogenic bone marrow transplantation has been shown to correct the hematologic and immunologic complications of CHS and has been proposed as the only possible curative treatment if performed early, before the onset of accelerated phase. However, it has not been shown to reverse or prevent a further neurological deficit.

Since the CHS disease is invariably lethal after entering the accelerated phase and early diagnosis may facilitate BMT as the only curative treatment, we suggest that careful examination of a well-prepared peripheral blood film is an essential investigation in all young children presenting with multiple recurrent infections or diagnosed with hemophagocytic lymphohistiocytosis.

Conflict of interest

The authors declare no conflicts of interest.

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