Chediak–Higashi Syndrome Presented as Accelerated Phase: Case Report and Review of the Literature

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Abstract Chediak–Higashi syndrome (CHS) is a rare autosomal recessive disease, characterized by partial oculocutaneous albinism, recurrent pyogenic infections (skin, mucosa and respiratory system), and neurologic deficit. The hallmark of this syndrome is the presence of abnormal intracytoplasmic giant granules in all granule containing cells including leukocytes in blood and bone marrow. A majority (85 %) of patients with CHS develop an accelerated phase consisting of a lymphoproliferative syndrome with hemophagocytosis and infiltration of most tissues. This phase is characterized by fever, jaundice, hepatosplenomegaly, lymphadenopathy, pancytopenia and neurological abnormalities. In this paper, we report a case of CHS presented as accelerated phase in a 9-month-old girl child.

Keywords Chediak–Higashi syndrome · Albinism · Primary granules · Pancytopenia · Lymphohistiocytic infiltration

Introduction

Chediak–Higashi syndrome (CHS) is a rare autosomal recessive disorder of all lysosomal granule containing cells with clinical features involving the hematologic and neurologic systems [1]. CHS was first described by Bequez-Cesar in

1943 and then by Steinbrinck in 1948 and ultimately by Chediak (1952) and Higashi (1954) [2]. The condition is characterized by partial oculocutaneous albinism, recurrent respiratory system and pyogenic infections, peripheral neuropathy. However, the diagnosis can only be made when the pathognomonic abnormal large granules are noted in the leucocytes and other granule-containing cells [1, 3]. Children affected by CHS are at great risk of death from infection during the accelerated phase. This phase is the most important and dangerous complication of the disease which occurs in 85 % of the cases. Characteristics of hemophagocytic lymphohistiocytosis are infiltration of visceral organs, fever, peripheral neuropathy, hepatitis, hepatosplenomegaly, lymphadenopathy, pancytopenia, coagulopathy and bleeding syndrome [2, 4]. In this paper, we report a case of CHS presented as accelerated phase in a 9-month-old girl child.

Case Reports

A 9-month-old girl was admitted with fever lasting for 1 week. His parents gave history of recurrent infections since birth. There was history of consanguineous marriage. There are two of his siblings had died with similar Clinical symptoms. On physical examination, patient was febrile (38 °C). He had pallor, hepatosplenomegaly and significant cervical lymphadenopathy. He also had partial cutaneous albinism and silver hair.

The relevant hematological findings on admission were a several anaemia (hemoglobin 79 g/L), normal leucocytes count (white blood cell count $15 \times 10^9/L$), and a thrombocytopenia (platelet count $79 \times 10^9/L$). Differential leucocyte count showed neutrophils 24 %, lymphocytes 69 %, and monocytes 7 %. On biochemical analysis, C-reactive protein was 5 mg/dL (N: <6 mg/dL), aspartate aminotransferase

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Fig. 1 Blood film showing abnormal giant cytoplasmic granules in lymphocytes

Fig. 3 Bone marrow smears showing pathognomonic giant granules in the leukocytes

Fig. 2 Bone marrow smears showing pathognomonic giant granules in the precursor cells of neutrophils

Fig. 4 Bone marrow aspirate shows increased number of histiocytes with active hemophagocytosis

128 U/L (N: <50 U/L), alanine aminotransferase 63 U/L (N: <45 U/L), lactate dehydrogenase 826 U/L (N: 150–500 U/L), serum triglyceride 3.73 g/dL (N: 0.9–1.7 g/dL), fibrinogen 2.3 g/L (N: 2–4 g/L), and ferritin 1,089 ng/mL (N: 7–140 ng/mL). Serological examinations for Epstein–Barr virus, rubella, cytomegalovirus, leishmania, toxoplasma, hepatitis B and C virus were negative.

In view of his clinical presentation and bicytopenia, he was referred for bone marrow aspiration to rule out hematologic malignancies. Examination of his peripheral blood film showed abnormal giant granules in the neutrophils and single large azurophilic granules in many lymphocytes (Fig. 1). These inclusions were also appreciated on bone marrow aspirate (Figs. 2, 3). Bone marrow aspirate also revealed prominent histiocytes and hemophagocytosis (Fig. 4). On the basis of his clinical presentation, peripheral blood film and bone marrow aspirate findings, the diagnosis

of CHS was established. Molecular studies were not carried out because of unavailability. Unfortunately, patient died after 2 months of hospitalization.

Discussion

Chediak–Higashi syndrome is a rare autosomal recessive disorder of all lysosomal granules-containing cells with clinical features involving the hematologic and neurologic systems. This syndrome consists of partial oculo-cutaneous albinism, recurrent pyogenic infection (usually skin, respiratory tract and mucous membrane), peripheral neuropathy [1, 2]. Other findings are platelet dysfunction with normal microtubules but absent or rare dense bodies [5]. The definitive diagnosis can be made on the pathognomonic intracytoplasmic giant granules on leukocytes [6, 7].

Currently, about 500 cases of the disease were reported at word. All age groups and races are involved equally but the onset of the disease begins after birth or less than 5 years of age [3].

The gene responsible for this defect was characterized in 1996 as the lysosomal trafficking regulator *LYST* or *CHS1* gene located on chromosome-1 (1q42-43) [8, 9]. Recently, 26 mutations in the *CHS1* gene have been described, including nonsense and missense mutations, deletions and insertions [10, 11]. This gene effects protein synthesis or/and maintenance of storage and secretory lysosomal granules of leukocytes and fibroblasts, dense bodies of platelets, azurophilic granules of neutrophils and melanosomes of melanocytes. Granules are composed of abnormal fusion of primary granules (azurophilic) with secondary granules (specific) [1, 8, 12]. Patients with CHS exhibit alterations in neutrophils including neutropenia, decreased deformability resulting in impaired chemotaxis and delayed phagolysosomal fusion resulting in impaired bactericidal activity. Lymphocytes contain large giant cytoplasmic granules and function poorly in antibody dependent cell mediated cytotoxicity of tumour cells. Natural killer cell function was also reduced [3, 10, 12]. A deficiency of granules containing serotonin and adenosine phosphate in platelets leads to defective platelet aggregation and prolonged bleeding time [5].

Typically patients with CHS present at an early age with recurrent pyogenic infection, partial oculo-cutaneous albinism, mild coagulation defect and progressive peripheral neuropathy [3, 13, 14]. There is recurrent infection especially pulmonary infection such as pneumonia in CHS patients. Other common infections are otitis media, dermal and mucosal infections. Affected patients are more susceptible to bacterial and fungal infections but have a normal resistance to viral infections [2, 3, 15]. Furthermore, *Staphylococcus aureus*, *Beta-Hemolytic Streptococci* and *Pneumococcal* species are more common pathogens. Partial oculocutaneous albinism is prominent and has been seen in skin, hair and eyes [1, 14, 16]. However, it can be presented completely, partially or absent. Ophthalmic symptoms include photophobia, horizontal or rotating nystagmus and increasing red reflex. Beside clinical characteristics, our case was diagnosed with typical microscopic investigation of hair but eye examination was normal [1, 17]. Neurological symptoms (peripheral neuropathy, paresthesia, stroke, coma and convulsion) manifest in approximately half of the affected individuals [2, 6].

Therefore, the diagnosis of CHS is based on the presence of giant abnormal granules in all granule containing cells including melanocytes, peripheral leukocytes and their bone marrow precursors, central and peripheral nerve tissue, fibroblast and hair and it is confirmed on the presence of *Lyst/CHS1* gene mutation [3].

The present patient presented with CHS in accelerated phase which has poor prognosis. This phase is the most

hazardous complication of CHS and 50–85 % of the patients are involved in the accelerated phase [2, 4, 13, 18]. Majority of the patients (90 %) may die in the first 10 years of their life. Hemophagocytic syndrome results from an inappropriate stimulation of macrophages in bone marrow and lymphoid organs, leading to phagocytosis of blood cells and production of high amounts of pro-inflammatory cytokines. It is characterized by clinical criteria (fever, hepatosplenomegaly, lymphadenopathy), biological features (pancytopenia, low fibrinogen, high plasma triglycerids, high ferritin and abnormal hepatic tests) and a diffuse lymphohistiocytic infiltration of the liver, spleen, lymph nodes, bone marrow and central nervous system [14, 16–19].

The differential diagnosis of CHS includes essentially with Griscelli syndrome and Hermansky–Pudlak syndrome. Griscelli syndrome is a rare disorder, has similar symptoms of CHS including partial cutaneous-ophthalmic albinism, humeral and cellular immune deficiency, exacerbated phase with pancytopenia, hemophagocytosis. Hermansky–Pudlak syndrome is a disorder of ocular and cutaneous albinism, bleeding diathesis and deposition of ceroid lipofuscin in various organs. However, giant leukocytic granules are the only major differentiating point between Griscelli and CHS as seen only in CHS [2, 3, 20].

Treatment options for CHS are limited and mainly symptomatic. Antibiotics are given to treat infections. High dose ascorbic acid (200 mg/kg) may improve the clinical course in some patients. Subsequently when accelerated phase occurs, etoposide (VP-16), steroids and intrathecal methotrexate have been tried. Bone marrow transplantation before the onset of accelerated phase is the only curable treatment which by replacing the defective hemopoietic system helps to eliminate the susceptibility to bacterial infection and the progression of the disorder to the accelerated phase [3, 13].

Conflict of interest We have no conflict of interest to declare.

References

1. Islam AS, Hawsawi ZM, Islam MS, Ibrahim OAH (2001) Chédiak–Higashi syndrome: an accelerated phase with hereditary elliptocytosis: case report and review of the literature. *Ann Saudi Med* 21(3–4):221–224
2. Tanzeel I, Lubna Z, Madeeha R, Aqsa N, Parveen Akhtar T, Iffat B (2012) Chédiak–Higashi syndrome presenting in accelerated phase. *J Coll Physicians Surg Pak* 22(8):539–541
3. Ghaffari J, Rezaee SA, Gharagozlou M (2013) Chédiak–Higashi syndrome. *J Pediatr Rev* 1(2):80–87
4. Sen R, Kataria SP, Agarwal R, Chhabra S, Mittal K (2013) Chédiak–Higashi syndrome presented as accelerated phase in a 3 year girl child: case report of a rare entity. *J Clin Case Rep* 3(6):1–3
5. Nurden P, Nurden AT (2008) Congenital disorders associated with platelet dysfunctions. *Thromb Haemost* 99:253–263

6. Farhoudi A, Chavoshzadeh Z, Pourpak Z, Izadyar M, Gharaogzou M, Movahedi M et al (2003) Report of six cases of Chediak–Higashi syndrome with regard to clinical and laboratory findings. *Iran J Allergy Asthma Immunol* 2:189–192
7. Masood A, Nadeem M, Aman S (2008) Chediak–Higashi syndrome—a case report. *Annals* 14(3):119–122
8. Nagel DL, Karim MA, Woolf EA, Holmgren L, Bork P, Misumi D et al (1996) Identification and mutation analysis of the complete gene for Chediak–Higashi syndrome. *Nat Genet* 14(3):307–311
9. Shyur SD, Hill HR (1996) Recent advances in the genetics of primary immunodeficiency syndromes. *J Pediatr* 129(1):8–24
10. Lakshman R, Finn A (2001) Neutrophil disorders and their management. *J Clin Pathol* 54:7–19
11. Zarzour W, Kleta R, Frangoul H, Suwannarat P, Jeong A, Kim SY et al (2005) Two novel CHS1 (LYST) mutations: Clinical correlations in an infant with Chediak–Higashi syndrome. *Mol Genet Metab* 85(2):125–132
12. Kjeldsen L, Calafat J, Borregaard N (1998) Giant granules of neutrophils in Chediak–Higashi syndrome are derived from azurophil granules but not from specific and gelatinase granules. *J Leukoc Biol* 64:72–77
13. Jayaranee S, Menaka N (2004) Chediak–Higashi syndrome: a case report. *Malaysian J Pathol* 26(1):53–57
14. Akbayram S, Akgun C, Basaranoglu M, kaya A, Balta A, Ustyol L et al (2011) A case of Chediak–Higashi syndrome presented with hemophagocytic lymphohistiocytosis. *Int J Hematol Oncol* 3(21):196–199
15. Nargund AR, Madhumathi DS, Premalatha CS, Rao CR, Appaji L, Lakshmidevi V (2010) Accelerated phase of Chediak–Higashi syndrome mimicking lymphoma—a case report. *J Pediatr Hematol Oncol* 32(6):223–226
16. Barton LM, Roberts P, Trantou V, Haworth C, Kelsey H, Blamires T (2004) Chédiak–Higashi syndrome. *Br J Haematol* 125(1):2
17. Roy A, Kar R, Basu D, Srivani S, Badhe BA (2011) Clinico-hematological profile of Chediak–Higashi syndrome: experience from a tertiary care center in south India. *Indian J Pathol Microbiol* 54(3):547–551
18. Miyamae T, Izaki S, Ikuta K, Yokota S, Yamanaka H (2013) Hemophagocytic lymphohistiocytosis developed in a Japanese boy with Chédiak–Higashi syndrome. *Nihon Rinsho Meneki Gakkai Kaishi*. 36(4):226–232
19. Sohaila F, Wajih AS, Mohd AA (2010) Chediak–Higashi syndrome: a rare clinical entity revisited. *J Indian Acad Clin Med* 11(2):144–145
20. Mancini AJ, Chan LS, Paller AS (1998) Partial albinism with immunodeficiency: Griscelli syndrome: report of a case and review of the literature. *J Am Acad Dermatol* 38:295–300