

Case Report

Chediak-Higashi Syndrome: Report of a Case with Uncommon Presentation and Review Literature

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Chediak-Higashi syndrome (CHS) is a very rare autosomal recessive immunodeficiency disorder characterized by partial albinism, recurrent pyogenic infections, and large granules in all granule-containing cells. The author describes a Thai girl who was the first case of CHS in Thailand. She presented in the accelerated phase of CHS, which leads to repeated infections and bleeding, often resulting in fatal outcome. Pancytopenias, hepatosplenomegaly, lymphohistiocytic infiltration in bone marrow and the abnormal characteristic granules in leukocyte clinched the diagnosis.

Keywords: Accelerated phase, Chediak-Higashi syndrome, Immunodeficiency disorder

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Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disease characterized by severe immunodeficiency, oculocutaneous albinism, bleeding diathesis, recurrent infections, progressive neurological defects and a lymphoproliferative syndrome. Since its original description in 1952, only approximated 200 reported cases worldwide have been described⁽¹⁻³⁾, most of them from the United States, Japan, Europe and Latin America. Most patients with CHS enter an accelerated phase that often results in death. The first accelerated phase of CHS may occur shortly after birth or several years later. Most patients undergo a variable period of recurrent infections before going into the accelerated phase. Therefore, primary presentation in the accelerated phase is unusual⁽⁴⁾. The author reports a case of CHS, first case from Thailand, who presented with the clinical accelerated phase of the disease. The actual diagnosis was established after the author found characterized abnormal granules in white blood cells in peripheral bloods and in bone marrow.

Case Report

A 1 ⁸/₁₂ year-old girl presented with a one-month fever, rhinorrhea and skin rash. She was first admitted to a province hospital 3 weeks previously as fever and petechiae lasted for 6 days. DHF was a

suspected initial diagnosis. Because of the persistent fever, antibiotics and PRC transfusion were given for 2 weeks. Then she developed a generalized skin rash, and pedal edema. Due to her clinical deterioration, her parents transferred their child to Children's Hospital in Bangkok. The child had been admitted to a province hospital for a few days with diarrhea when she was 6 month-old. Fig. 1 shows the consanguinity in the parents. She was the only child of the parents. On physical examination, she had silvery hair, whitish eyebrows and eyelashes, spot hypopigmentation and hyperpigmentation of skin sun exposure. Her vital signs were T 39°C, pulse rate 150 bpm., and respiratory rate 58/min. In addition, she had moderate pallor, hepatomegaly (5 cm below RCM), and splenomegaly (6 cm below LCM), but no clinical jaundice or lymphadenopathy.

Investigations showed pancytopenia in CBC, Hb 7.5 g/dL, platelet count 27 x 10³/L. Though total WBC was within normal range (5,100/L), there was neutropenia (ANC 408/L) with predominate lymphocytes (90%). Serial blood culture did not show any bacterial growth. Chest X ray showed interstitial infiltration with minimal RLL pneumonia. The bone marrow finding was mildly hypercellular with slightly increased histiocytes and hemophagocytic activity, no abnormal blast. Large granules were seen in the cytoplasm of granulocytic series including monocytes as shown in Fig. 2 and 3.

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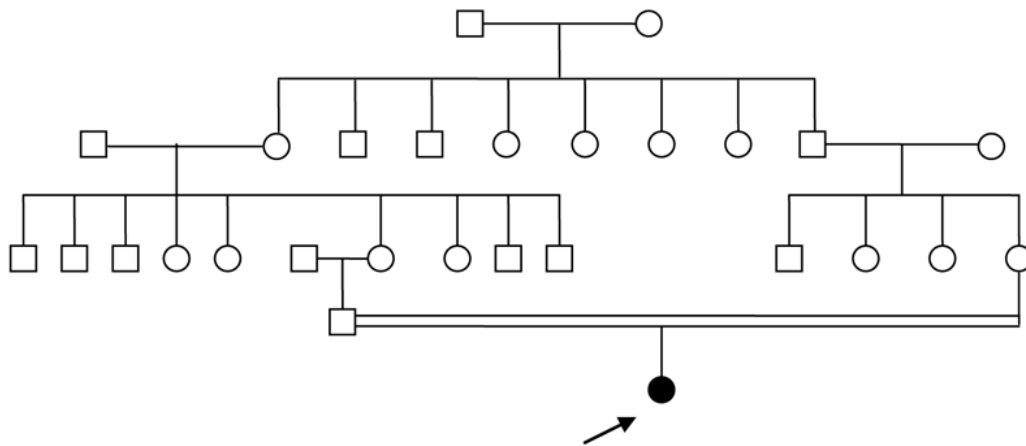


Fig. 1 Pedigree of patient's family

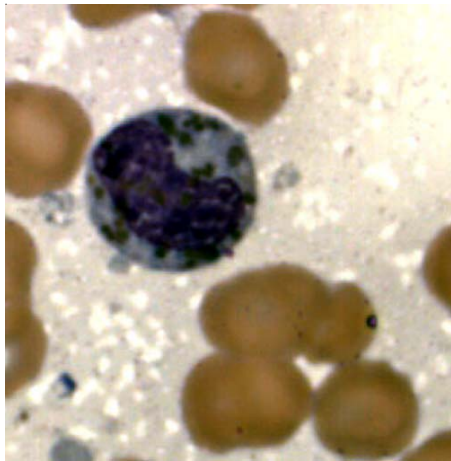


Fig. 2 Monocyte

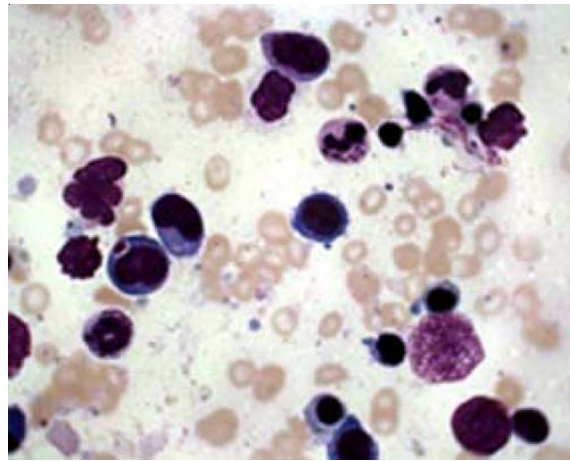


Fig. 3 Granulocytes and Monocyte in BM

Based on the clinical presentation and hematologic findings, a diagnosis of accelerated phase of CHS was made. The patient was treated with empirical antibiotics, and vitamin C. High dose methylprednisolone and prednisolone were given for treatment of the accelerated phase. Afebrile intervals with improvement of clinical well being and reducing in hepatosplenomegaly were noticed as brief clinical responses to therapy. During the process of HLA typing while searching for a donor for BMT, the child was readmitted due to severe pneumonia, which progressed to ARDS. She succumbed to her illness after 6 days of hospitalization. An autopsy was refused by the parents.

Discussion

CHS is a very rare autosomal recessive disorder that affects the lysosomes or lysosome-like

organelles of cells within multiple tissues throughout the body. The hallmark of CHS is the presence of singular or characteristic multiple intracellular inclusions in the neutrophils and other cells. These abnormal inclusions in CHS neutrophils are unable to adequately metabolize and digest microbes. The abnormalities are also accompanied by defective immunity, especially in the NK cells and neutrophils, which lead to recurrent infections in early childhood. The average life span of children affected by CHS is 6 years. In natural history, the disease is characterized by a variable period of recurrent infections followed by a fatal lymphohistiocytic infiltration, which is known as the accelerated phase of CHS. It usually occurs in the second decade of life, culminating in a fatal outcome^(3,4). Most children with CHS receive early attention because of troublesome infections, hence initial presentation in the

accelerated phase as this case is rare⁽⁵⁾. Though the common organism associated with infections in the chronic stable phase of the disease are *S.aureus* and *Streptococcus spp.* Epstein-Barr virus (EBV) is implicated in the accelerated phase. It is believed that the inability to clear the EBV infection leads to a state of constant lymphoproliferation, as seen in the phase of disease acceleration⁽⁶⁾. The same virus may be responsible for the hemophagocytic syndrome⁽⁷⁾.

The CHS gene was identified in 1996 and has been mapped onto chromosome 1q42-q44⁽⁸⁾, a region codes for a protein. However, its function remains unknown^(9,10). Referring to a recent study⁽¹¹⁾, the results suggested that the CHS/Beige protein interacted with at least two different partners and affects cellular events, such as nuclear PtdIns(4,5)P₂ localization, in addition to regulating lysosome size. Moreover, a study showed that the apparent allelic genotype-phenotype relationship among the various clinical forms of CHS⁽¹²⁾. Homozygous protein-null alleles were associated with severe childhood CHS, and at least some homozygous missense mutant alleles were associated with clinically milder forms of the disorder.

The treatment of CHS is still controversial. Parenteral vitamin C administered in the stable phase may normalize neutrophils bactericidal activity⁽¹³⁾, but it has little benefit in the accelerated phase. In some patients, high dose methylprednisolone with or without splenectomy may be effective⁽¹⁴⁾. Chemotherapy with vincristine can induce transient remission of the accelerated phase, but relapses become less responsive to the treatment. Receiving G-CSF maintenance treatment in a case of CHS prevented further infectious episodes within a 6 month period of treatment in a report⁽¹⁵⁾. Allogeneic bone marrow transplant has been proposed as the only possibly curative treatment when performed early, before the onset of the accelerated phase^(5,16-18).

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รายงานผู้ป่วยโรค Chediak-Higashi syndrome

สมใจ กาญจนางศ์กุล

Chediak-Higashi syndrome เป็นโรคที่ถ่ายทอดทางพันธุกรรมแบบยีนด้อยซึ่งพบผู้ป่วยโรคนี้ได้น้อยรายทั่วโลก ผู้ป่วยมีโอกาสเสี่ยงต่อการติดเชื้อได้ง่ายเนื่องจากมีภาวะภูมิคุ้มกันบกพร่อง มีผิวเผือกหรือผิวสีอ่อน ภายในซัยโตพลาสซึมของเม็ดเลือดขาวหลายชนิดจะเห็นแกรนูลส์ขนาดใหญ่ติดสีเข้มเป็นลักษณะเฉพาะที่ช่วยในการวินิจฉัยโรคนี้ ผู้เสนอได้รายงานผู้ป่วยเด็กหญิงไทยที่มาพบแพทย์ด้วยอาการของระยะ *accelerated phase* คือ ไข้ ชีต เกิดเลือดต่ำ ตับและม้ามโต ในไขกระดูกพบ *lymphohistiocytosis* จากการตรวจพบแกรนูลส์ที่ผิดปกติภายในเม็ดเลือดขาวทำให้ผู้ป่วยได้รับการวินิจฉัยโรค *Chediak-Higashi syndrome* เป็นรายแรกของประเทศไทย