A Case of Chediak-Higashi Syndrome Presented with Hemophagocytic Lymphohistiocytosis

Sinan AKBAYRAM[1], Cihangir AKGUN[1], Murat BASARANOGLU[1], Avni KAYA[1], Gunay BALTA[2], Lokman USTYOL[1], Osman YESILMEN[1], Ibrahim DEGER[1], Ahmet F. ONER[3]

[1] Yuzuncu Yil University Faculty of Medicine, Department of Pediatrics, Van
[2] Hacettepe University Faculty of Medicine, Department of Pediatric Hematology, Ankara
[3] Yuzuncu Yil University Faculty of Medicine, Department of Pediatric Hematology, Van, TURKEY

ABSTRACT

Chediak Higashi syndrome, is a rare autosomal recessive disorder characterised by oculocutaneus albinism, recurrent respiratory system infections and other pyogenic infections. Hemophagocytic lymphohistiocytosis can develop in any time of the life in patients with Chediak Higashi syndrome. A 14-month-old girl patient was diagnosed as hemophagocytic lymphohistiocytosis with the laboratory findings of pancytopenia, high levels of triglyceride and ferritin, hypofibrinogenemia, low ratio of natural killers in lymphocyte subtypes, and with determined macrophages that made hemophagocytosis in recurrent bone marrow aspirates. The treatment protocol of hemophagocytic lymphohistiocytosis 2004 was administered. During the maintenance treatment, recurrence was developed. In the second bone marrow examination, the diagnosis of Chediak Higashi syndrome was made with determined intracytoplasmic giant granules. Hair analysis result was meaningful for Chediak Higashi syndrome. In this report, we would like to emphasize the condition that especially in early infants, Chediak Higashi syndrome presenting with hemophagocytic lymphohistiocytosis may be misdiagnosed because of the uncertain clinical findings and this can be the result of resistance to treatment.

Keywords: Albinism, Chediak Higashi syndrome, Hemophagocytic lymphohistiocytosis

ÖZET

Hemofagositik Lenfohistiositoz Kliniği ile Prezente Chediak-Higashi Sendromu Olgusu

Chediak Higashi sendromu (CHS) nadir görülen otozomal resesif bir hastalıktır. Hastalık okülokutanöz albinizm ile tekrarlayan solunum sistemi ve diğer piyojenik enfeksiyonlar ile karekterizedir. CHS'li hastalarda hayatın herhangi bir döneminde hemofagositik lenfohistiositoz gelişebilir. On dört aylık kız hasta pansitopeni, trigliserit ve ferritin düzeylerinin yüksek olması, hipofibrinojenemi, lenfosit alt tiplendirmesinde doğal öldürücü hücre oranlarının düşük gelmesi ve tekrarlayan kemik iliği incelemesinde hemofagositoz yapmış makrofajlar görülmesi üzerine hemofagositik lenfohistiositoz olarak kabul edildi. Hemofagositik lenfohistiositoz (HLH 2004) tedavi protokolü başlandı. Olgu idame tedavisi aşamasında iken nüks etti. İkinci kemik iliği incelemesinde intrastoplazmik dev granüllerin görülmesi ile CHS tanısı kondu. Bakılan saç analizi CHS ile uyumlu bulundu. Bu makale ile hemofagositik lenfohistiositoz tanısında özellikle erken bebeklikte kliniğin tam olarak ortaya çıkmaması nedeni ile CHS'nin atlanababileceği ve bu olguların tedaviye dirençlerinin önemli bir problem oluşturduğunun vurgulanması amaçlanmıştır.

Anahtar Kelimeler: Albinizm, Chediak Higashi sendromu, Hemofagositik lenfohistiositoz

INTRODUCTION

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder characterized by oculocutaneus albinism, recurrent respiratory system and pyogenic infections and intracytoplasmic giant granules on leukocytes.[1] Incidence of the disease is 3/15.000 in patients admitted to hospital.[2] Accelerated phase occurs in 85% of the cases. Characteristics of hemophagocytic lymphohistiocytosis (HLH) are infiltration of visceral organs, fever, peripheral neuropathy, hepatitis, hepatosplenomegaly, lenfadenopathy, pancytopenia, coagulopathy and hemorrhage. Pseudomembrane may be developed at gingiva and buccal mucosa.[3-6] In this article, we report a case of CHS unusually presented with HLH.

CASE PRESENTATION

A 14-month-old girl was admitted with fever and cough for 4 days and abdominal distension for one month. On physical examination, her general condition was good and consciousness was clear. Her skin and conjunctivas were pale and petechial rashes were noted on skin. She had 6 kg (25-50 percentile) of body weight, 61 cm (25-50 percentile) of height, and 42 cm (50-75 percentile) of head circumference. Body temperature was 37.3^{0}C. Anterior fontanel was of 4 x 3 cm. Bilateral fine rales were noted on middle zones of lungs. She also had tachycardia, abdominal distention and 5 cm hepatosplenomegaly. Theremain physical examination findings were unremarkable.

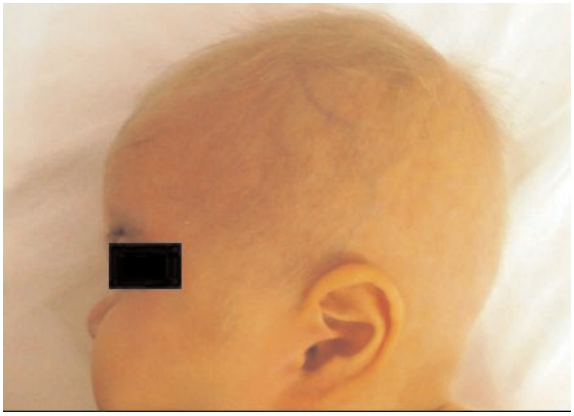
On laboratory examination, urinary analysis was unremarkable. Hemoglobin, white blood cell count and thrombocyte count were 8.9 g/dL, 6900/mm^3 and 20.000/mm^3, respectively. On peripheral blood smearing, the ratio of lymphocyte and polymorphonuclear leukocyte were 72% and 28%, respectively. Erythrocytes were normocytic-normochromic, thrombocytes were scarce but no atypical cell was noted. Sedimentation rate was 28 mm/h (N: 0-20 mm/h), and C-reactive protein was 35 mg/dL (N: 0-3 mg/dL). On biochemical analysis, aspartate aminotransferase was 106 U/L (N: 15-55 U/L), alanine aminotransferase 34 U/L (N: 5-45 U/L), lactate dehydrogenase 756 U/L (N: 150-500 U/L), gamma glutamic transferase 204 U/L (N: 5-32 U/L), serum triglyceride 300 mg/dL (N: 32-99 mg/dL), fibrinogen 98 ng/dL (N: 200-400 ng/dL), and ferritin was greater than 1500 ng/mL (N: 7-140 ng/mL). Prothrombin time was 26 sec (N: 11-15 sec), and activated partial thromboplastin time was 48 sec (N: 25-35 sec). Serum vitamin B_{12} level was greater than 1000 pg/mL (N: 140-700 pg/mL). Serological examinations for Ebstein-Barr virus, rubella, cytomegalovirus, toxoplasma, Varisella-Zoster virus, hepatitis B virus were negative. Salmonella and brucella tube agglutination tests were negative. On bone marrow aspiration smears, hemophagocytic histiocytes were diagnosed; CD16+56 was positive, CD3 was negative, ratio of natural killer cells was 4.6% (N: 6-29%). Intracytoplasmic giant granules, characteristic for CHS were observed on the 2nd bone marrow aspiration smears.

The patient was hospitalized with the diagnosis of pneumonia and HLH. Aside from intravenous antibiotherapy, fluid replacement, erythrocyte suspension was given. HLH-2004 protocol including dexamethasone, etoposide and cyclosporine A was administrated. On the 11th week of maintenance therapy, a recurrence was noted and HLH-2004 treatment protocol was re-initiated. During that period, it was noticed that her hairs were thinned, and faded (Image 1). Hair analysis was consistent with CHS. Molecular genetic analysis for HLH studied at Hacettepe University Pediatric Hematology Genetic Analysis Laboratory showed perforin-1, syntaxin-11, and UNC13D gene mutations.

DISCUSSION

CHS is a generalized cellular function disorder, which is autosomal recessive inherited, rarely observed and inclined to join granules at the cell cytoplasm.[7] Dysfunction of granulated cell dispersed to the entire body is the cause of the symptoms of this disease. Particularly, hematopoietic tissue cells, peripheral nerve cells, central nervous system neurons, renal tubular cells, vein endothelium and fibroblasts in which granules present are influenced.[8,9]

Disease proceeds in two periods as stable and accelerated. In the stable period, clinical situation is milder. In accelerated phase, lymphohistiocytic infiltration, fever, peripheral neuropathy, hepatitis, hepatosplenomegaly, lenfadenopathy, pancytopenia, coagulopathy and hemorrhage are seen. On gingivitis and buccal mucosa, pseudomembranes may occur. Accelerated phase occurs in 85% of ca-



Picture 1. In our case, thin hairs turning into light brown from brown.

ses.[3-6] Clinical inception of accelerated phase may occur in short time after birth or delay four years. Accelerated phase was first defined at 1964 and its pathophysiology is not well known.[10] Majority of the patients (90%) may die in the first ten years of their life because of pyogenic infection, hemorrhage, complications at accelerated phase. Ten percentage part does not transmit a disease till the puberty. However, they become dependent on other people because of severe neurological complications.[11,12] Moreover, accelerated phase may be confused with familial erythrophagocytic lymphohistiocytosis syndrome.[13]

In HLH report published by Histiocyte Society, it is indicated that because CHS resembles HLH, good results can be obtained through HLH therapy. However, it should be evaluated out of HLH.[14] The case was fourteen months old and during first application, because lymphohistiocytic infiltration was observed (it fulfills seven criteria of HLH diagnosis) in bone marrow aspiration, and also because of fever, splenomegaly, bicytopenia (anemia and thrombocytopenia), hipertrigliceridemia, hipofibrinogenamia, high ferritin, low naturel killer cells levels at sublymphocyte classifications, she was diagnosed as HLH. In the second bone marrow investigation, because intracytoplasmic giant granules were observed, hemophagocytic syndrome findings were present, hairs were thinned and blurred and hair analysis supported CHS, it was accepted as CHS. Although, the initially normal hairs that blur over time were not characteristic of CHS, it was observed at clinical studies. The case was regarded as accelerated phase following non-reducing fever, hepatitis, hepatosplenomegaly, lenfadenopathy, pansitopenia, pseudomembrane which formed inside mouth. For people having reduced skin and hair pigmentation and transmit frequent infections, if giant azurophilic cytoplasmic inclusions are present in histologically granular cells, CHS diagnosis should be considered. Essential diagnosis is made by the detection of CHS1 gene mutation at 1q43 in molecular basis. Although other undefined mutations may be considered in cases as CHS, they have different mutations.[15] Beside clinical characteristics, our case was diagnosed with typical microscopic investigation of hairs and clusters of pigments were observed along hair body. However, due to technical reasons, chromosome analysis could not be sent.

In CHS, melanosome caused diffused pigmentation abnormalities leads to oculocutaneous albinism which is a characteristic finding.[8] Eye examination was normal; albinism was present at the skin.

In patients, generally immunity is reduced against infections and inclination for particularly pyogenic infections is raised.[9] Our case already received treatment three times for respiratory tract infection and two times for sepsis.

In CHS, there is an inclination for haemorrhage related to thrombocyte dysfunction.[16] In our case, thrombocytopenia and abnormalities in coagulation tests were detected and ecchymotic lesions were present on the skin.

In more than 85% of the cases, hepatosplenomegaly, thrombocytopenia, hipertrigliceridemia, hipofibrinogenemia are detected.[9,17] In our case, fever, haemorrhage, anaemia, neutropenia, thrombocytopenia, low fibrinogen level, high transaminase level, hipertrigliceridemia, hyperbilirubinemia, hystiocytes demonstrating erythrophagocytosis in bone marrow aspiration were detected.

Some neurological disorders emerge as a result of giant granules forming at schwann cells and other central nervous system cells and deformation of cortical nerve fibers.[18] In some cases, motor and sensual damages may form. Ataxia, loss of power, decrease at motor conduction may be added to the list.[17,18] Motor development and examination of our case was normal. There was no specific treatment for CHS. Infections were treated. Bleeding diathesis was treated. Accelerated phase should be under

control. Chemotherapy provides temporary remedy. Stem cell transplantation may provide partial or complete wellness.[19] In our case, intravenous double antibiotherapy, fresh frozen plasma, erythrocyte suspensions and in accordance with HLH-2004 protocol dexamethasone, etoposide and cyclosporine A were used.

Fischer and Griscelli reported that they provided remission at eight patients out of eleven by using etoposide and methylprednisolone combination.[16] In three of them, relapse occurred, two relapsed cases died, third case died in 45 days although HLH suitable bone marrow transplantation was applied.

Bone marrow transplantation was applied to four patients demonstrating remission; the first one died in 65 days due to cytomegalovirus infection, in other there patients accelerated phase occurred after 77, 63 and 59 months respectively.[9] Our patient was positively responsive to chemotherapy in short time however, during maintenance therapy it relapsed. The aim of bone marrow transplantation applied at CHS is to retrieve haematological trends at the cells and reforming immunity by adjusting the natural killer cell activity.[17] In our case, bone marrow transplantation was planned. Our patient was kept in control for eight months and it was carried out in our polyclinic according to HLH-2004 protocol.

As a result, CHS is a rare and progressive disease. In nursling infants with albinism, this syndrome should be considered, diagnosis should be ensured with further investigations and primarily, bone marrow transplantation should be proposed beside supplementary therapy.

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Correspondence

Dr. Sinan AKBAYRAM

YYÜ Tıp Fakültesi Araştırma Hastanesi

Çocuk Sağlığı ve Hastalıkları Servisi Van / TURKEY

Tel: (+90.432) 215 04 73 / 1137

e-mail: drsinanakbayram@gmail.com