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CHEDIAK-HIGASHI SYNDROME

Emad uddin Siddiqui¹, Shaheena Hanif²

ABSTRACT

Chediak Higashi Syndrome is a rare inherited autosomal recessive disorder of immune system. Susceptibility to infection due to phagocyte dysfunction ranges from recurrent skin infection to overwhelming fatal systemic infection. A five years old male child was admitted on 31st March 2006 with the complaints of pallor, fever & ear discharge for 6 month. He was treated by several medications but had temporary relief. The ear discharge was bilateral, foul smelling and of yellowish color. Past history was significant with episodes of abscess involving the different parts of body. Myeloid precursors shows giant, purple stained granules mainly in metamyelocytes, band cells and mature neutrophils.

KEY WORDS: Chediak-Higashi syndrome, Pediatric, recurrent skin abscess.

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INTRODUCTION

This was in 1943 when Beguez briefly outline the disease followed by Stein Brinck (1948) and then by Chediak (1952) & Higashi (1954). This is a rare inherited autosomal recessive disorder of immune system characterized by increase susceptibility to infections due to defective granulation of neutrophil and abnormal function of natural killer cell with bleeding diathesis, partial oculocutaneous albinism, progressive peripheral neuropathy and the tendency to develop a life threatening lymphoma like syndrome.¹ Susceptibility to infection from phagocytic dysfunction ranges from mild recurrent skin infections to overwhelming

fatal systemic infection. Affected patients are more susceptible to bacterial and fungal infections, but have a normal resistance to viral infections. Majority of patients are diagnosed in infancy due to the severity of the infection or the unusual presentation of the organism, but some escape the diagnosis until adulthood.

CASE REPORT

This is a case of five years old male child who was admitted on 31st March 2006 with the complaints of pallor, fever & ear discharge for last six months. He received multiple drugs with several antibiotics but had temporary relief. The ear discharge was bilateral, foul smelling & yellowish green in colored.

Past history was significant; he had multiple abscesses involving the different parts of body at different occasions. The last abscess appeared some two months back affecting the injection site and took one month to resolve even with antibiotics. There were multiple old healed infected areas on face and limb. He had been treated for repeated episodes of diarrhoea and pneumonia in past with oral and injectable antibiotics. He had also been transfused several times in the last few months because of pancytopenia. He was vaccinated according to EPI schedule. There was no significant

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family history. His birth was uneventful. His height and weight was below 5th centile. He was febrile (101 F) pulse of 120/min and R/R of 32/min. The child was anemic with de-pigmented skin rash and hairs, while cervical lymph nodes were enlarged. Liver was three cm palpable below the right costal margin, on tender, smooth surface and sharp border, spleen was also palpable 3 cm along its long axis. Other system was intact. His gait was normal.

His initial CBC shows Hb of 6gm/dl, TLC of 1500 (neutrophils of 481/cumm, lymphocytes of 950/cumm) Platelets 2000/cumm. Serum Complement {C3-1.51(0.9-1.8), C4-0.26(0.1-0.4)} and immunoglobulin levels were {IgG-9.74 (7-16), IgA-0.29 (0.7-4.0), IgM-0.88 (0.4-2.3)}. Bone marrow D/R shows all three cell lines with M:E ratio of 15:1. Erythropoiesis shows dyserythropoietic changes including nuclear cytoplasmic disproportion. Myeloid precursors shows giant, purple stained granules mainly in metamyelocytes, band cells and mature neutrophils. These findings are suggestive of Chediak Higashi syndrome.

He was treated with antibiotics, high dose Ascorbic acid and transfused with packed cell and platelets. Patient was discharged safely. He continued the follow-up for six months before he was lost the follow up.

DISCUSSION

The gene of CHS (Chediak-Higashi Syndrome) is located on chromosome 1, q42-44. This gene effects protein synthesis or/and maintains of storage & secretory granules lysosomal of leukocytes and fibroblast, dense bodies of platelets, azurophils granules of neutrophils and melanosomes of melanocytes all are involved.² The defective gene, called LYST, has been identified.³ Deficiency of proteolytic enzymes, impaired function of polymorph nuclear cells due to abnormal micro tubular assembly and impaired chemotaxis all leads to impaired immunity.

Phagocytic disorders may be divided into extrinsic and intrinsic defects: Extrinsic defects include opsonic abnormalities secondary to

deficiencies of antibody and complement factors leading to neutropenia by suppression of the production of granulocytes, or to a decrease in the number of circulating neutrophils by the presence of autoantibody directed against neutrophil antigens.

Intrinsic disorders of granulocytes results from defects in granulocyte killing ability and those that inhibit chemotaxis (cell movement). Intrinsic disorders of phagocytic killing ability include chronic granulomatous disease, glycogen storage disease type Ib, Chediak-Higashi syndrome, and specific granule deficiency.⁴

Almost all cells of patients with CHS shows some form of markedly abnormal "giant" cytoplasmic granules which are formed by the inappropriate fusion of lysosomes and endosomes. Neutrophils are mildly depressed and have impaired chemotaxis and intracellular killing, natural killer cell function are also impaired. Similar finding were found in the microscopic examination of bone marrow aspirates of our patient. His peripheral smear also reveals neutropenia. Same for melanocytes with failure to properly disperse the giant melanosomes, resulting in hair shaft devoid of pigments. This leads to appearance of skin and hair follicle that is lighter than expected as was in our case.

These children are more prone to recurrent skin infections. Other sites of involvement are mucous membrane, lung and intestine. Affected children are prone to have gram positive and gram negative organism. The neuropathy is usually sensory, motor may also be involved associated with ataxia and it may be the late presentation. Ataxia was not present in our case, it might be due to early presentation.

The most devastating symptoms are lymphoma like presentation characterized by pancytopenia, high grade fever, lymphohistiocytic infiltration of liver, spleen and lymph nodes. Death among patients with CHS is often due to sequelae of infection. Patients who do not succumb eventually enter the "accelerated phase" of the disease characterized by massive lymphohistiocytic infiltration of virtually

all organ systems, resulting in pancytopenia and even more profound immune deficiency.

When there is suspicion the diagnosis of CHS can be established by examination of a stained peripheral blood smear demonstrating abnormal giant granules in neutrophil, supported by the suggestive history and clinical findings.⁵ High dose Ascorbic acid (200mg/kg) may improve the clinical course in some patients.¹ CHS is treated by prophylaxis and aggressive therapy of bacterial infections. Splenectomy has been used with some success in the accelerated phase.⁶ We started the conventional therapy in our patient who initially showed some improvement but ultimately lost during follow up.

Bone marrow transplantation (BMT) is the only curative treatment from a HLA compatible matched donor. The BMT reconstitutes normal haematopoietic and immunologic function and correct the natural killer cell deficiency in patients. BMT does not improve the neuropathy.¹

BMT has been successful in a number of cases. One series of 10 patients with CHS reported that six out of seven patients who received a HLA-identical marrow and one out of three recipients of HLA-non identical marrow remained healthy at a median follow-up of 6.5 years (range of 1.5 to 13 years).⁷

An HLA-identical sibling bone marrow transplant was done for a patient with Chediak-Higashi syndrome. The preparative regimen included intravenous fludarabine

(40mg/m²/dx4) and busulfan (130 mg/m²/dx4). Busulfan was given once daily. Pharmacokinetic studies showed the area under the concentration-time curve of the once-daily intravenous busulfan was similar to that seen with the total daily dose administered with an every-6-hourly regimen. Toxicity was minimal. Myeloid engraftment occurred on day +17 and donor chimerism was complete. Fludarabine and once-daily intravenous busulfan is well tolerated and is adequate for engraftment of sibling transplant in Chediak-Higashi syndrome.⁸

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