Case Report

Chediak Higashi Syndrome with Recurrent Upper Respiratory Tract Infection

Kafil Akhtar, *Asst. Professor,*
Department of Pathology, Jawaharlal Nehru Medical College,
Aligarh Muslim University, Aligarh (U.P), India.

Sohaila Fatima, *Lecturer*,

Arshi Malik, *Asst. Professor*,

Sara Afaq, *Asst. Professor*

— College of Medicine, KKU, Abha, KSA.

Rana K Sherwani, *Professor,*
Department of Pathology, Jawaharlal Nehru Medical College,
Aligarh Muslim University, Aligarh (U.P), India.

Abstract

A four-year old child presented with history of recurrent infections since birth, mostly upper respiratory tract infections or sino-pulmonary involvement and moderate grade fever with symptomatic relief on antibiotics and antipyretic medications. We present this case which was diagnosed as respiratory tract infection with neutropenia consistent with Chediak-Higashi syndrome(CHS), with a brief review of this rare genetic clinical entity.

Keywords

respiratory tract infection, neutropenia, chediak-higashi syndrome

Introduction

Chediak Higashi Syndrome (CHS) is a rare childhood autosomal recessive disorder of immune system that affects multiple systems of the body[1]. Patients exhibit hypopigmentation of skin, eyes and hair, prolonged bleeding time, recurrent infections, easy bruisability, abnormal natural killer cell function and peripheral neuropathy. Mutations have been found in CHS1 gene or LYST and are localized to bands $1q_{42-43}$ which leads to abnormal intracellular protein transport[2].

The disease is often fatal in childhood as a result of infection or an accelerated lymphoma like phase and very few patients live to adulthood. Progressive neurological dysfunction may be the dominant feature in a few of these patients.

Case Summary

A four-year old child presented to the Pediatric ward with fever, cough and ulcers in the mouth. His father gave history of recurrent infections since birth, mostly upper respiratory tract infections or sino-pulmonary involvement with moderate grade fever with symptomatic relief on antibiotics and antipyretic medications. Family history was not contributory. No other sibling or family member had similar frequent infections.

Address for correspondence: Dr Kafil Akhtar, Assistant Professor, Department of Pathology, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, (U.P.), India. E-mail: drkafilakhtar@gmail.com

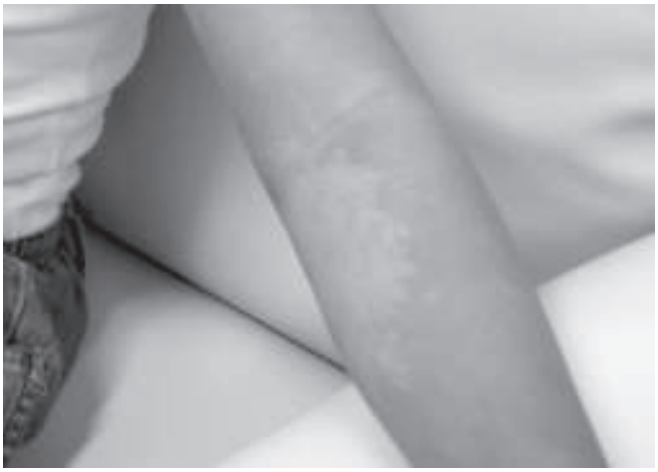

Fig. 1
CHS: Gross photograph showing hypo-pigmented patches in the skin of the forearm

On physical examination, the child was lean and thin built with light colored hair,scattered hypopigmented patches in the skin (**Fig. 1**) and cervical lymphadenopathy. Oral examination revealed congested tonsils and aphthous ulcers (**Fig. 2**) with oral temperature of 101.3°F (38.0°C).

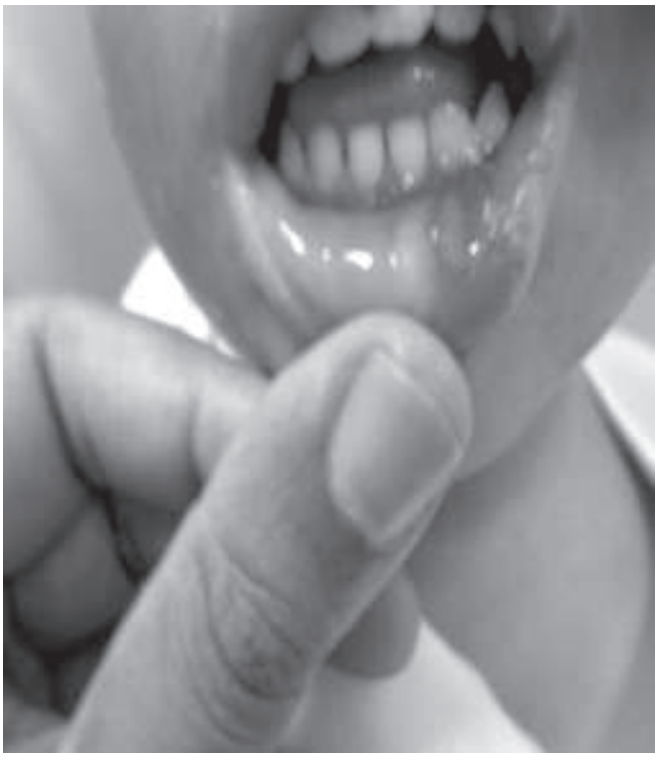

Fig. 2
CHS: Gross photograph showing aphthous ulcer in the oral mucosa

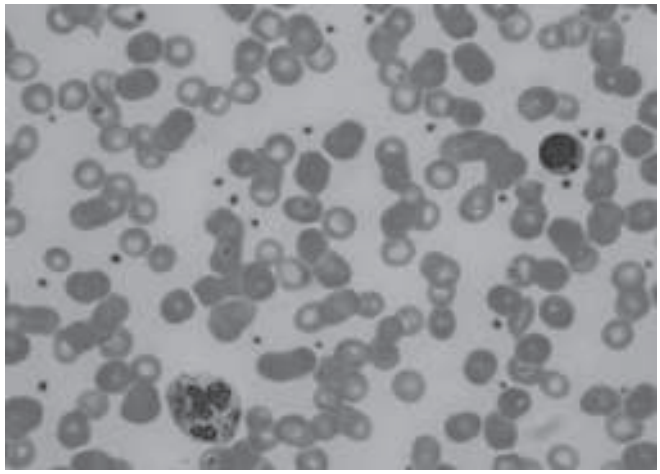

Fig. 3
CHS: Peripheral blood smear showing prominent coarse granules in neutrophils along with dot like inclusions in lymphocytes

His pulse was regular with 90 beats per minute and blood pressure was 100/80 mm Hg. Lungs showed bilateral crepitations on auscultation and central and peripheral nervous system examination was unremarkable.

The laboratory analysis showed a decreased total leucocyte count of 3000 cells/cc with marked neutropenia and prominent coarse granules in neutrophils along with dot like inclusions in lymphocytes on peripheral blood examination (**Fig. 3**) with hemoglobin level of 6.0 gm%. The patient was diagnosed as respiratory tract infection with neutropenia consistent with Chediak-Higashi syndrome and treated in the emergency department with complete bed rest, intravenous fluids, antibiotics, and antipyretics. He was later admitted to the hospital for continuous monitoring, blood transfusion therapy, intravenous injections of colony stimulating factors and bone marrow transplantation. Our patient is doing well after 6 months of follow up period.

Discussion

The diagnosis of Chediak-Higashi Syndrome (CHS) was made on the basis of the patient's history, results of the physical examination and peripheral blood smear findings, which showed the presence of neutropenia; and characteristic giant granules in neutrophils, eosinophils and a single granule in lymphocyte. Our patient presented with aphthae, gingivitis, lymphadenopathy, recurrent sino-pulmonary infections and fever with light colored hair and

scattered hypopigmented patches in the skin. Quite similarly Saez *et al*[3] and Ward *et al*[4] have reported that sign and symptoms appear soon after birth and include lymphadenopathy, aphthae, gingivitis, hyperhidrosis, jaundice, extensive pyoderma, recurrent sino-pulmonary infections and fever unrelated to recognizable infection. Severe gingivitis, oral mucosal ulcerations and periodontal disease are also common[5,6]. Infants born with CHS have non-pigmented skin (similar to albinos) but in patchy distribution, blonde hair and blue eyes[3]. Chediak-Higashi syndrome affects all races and Al-Khenaizan[7]suggests that Chediak-Higashi syndrome may be underreported in persons of darker-skinned races. There are several manifestations of Chediak–Higashi syndrome as mentioned above; however, neutropenia seems to be the most common[7].

Chediak Higashi Syndrome (CHS) was described by Beguez Cesar in 1943, Steinbrinck in 1948, Chediak in 1952 and Higachi in 1954. It is a rare autosomal recessive immunodeficiency disorder that affects multiple systems of the body.[1] It occurs in humans, cattle, white tigers, blue Persian cats and the only known captive albino orca[8]. It is named for the Cuban physician and serologist Alexander Moisés Chédiak and the Japanese pediatrician Otokata Higashi[1].

The Chédiak-Higashi syndrome locus on human chromosome 1 encodes a lysosomal trafficking regulator, formerly termed *LYST* (currently termed *CHS1*), which is defective in patients with CHS.[1,2] It is characterized by abnormal intracellular protein transport. The Chédiak-Higashi syndrome gene affects the synthesis and/or maintenance of storage/secretory granules in various types of cells. Lysosomes of leukocytes and fibroblasts, dense bodies of platelets, azurophilic granules of neutrophils, and melanosomes of melanocytes are generally larger in size and irregular in morphology, indicating that a common pathway in the synthesis of organelles responsible for storage is affected in patients with Chédiak-Higashi syndrome. The impaired function in the polymorphonuclear leukocytes may be related to abnormal microtubular assembly[9]. A defect in granules found in certain types of white blood cells causes immune system problems.[10] Defective melanization of melanosomes occurs in oculocutaneous albinism associated with Chédiak-Higashi syndrome[9].

The CHS protein is expressed in the cytoplasm of cells of variety of tissues and represent an abnormality of organellar protein trafficking. Morbidity results from patients succumbing to frequent bacterial infections or to an accelerated-phase lymphoproliferation into the major organs of the body[10,11,12]. This lymphoma like stage is precipitated by viruses, particularly by infection by the Epstein-Barr virus. It is associated with anemia, bleeding episodes, and overwhelming infections leading to death. Infections most commonly involve the skin, the lungs, and the respiratory tract and are usually due to staphylococcus aureus, streptococcus pyogenes, and pneumococcus species. In these patients, a progressive neurologic dysfunction may be the dominant feature. Neurologic involvement is variable but often includes peripheral neuropathy. The mechanism of peripheral neuropathy in Chédiak-Higashi syndrome has not been completely elucidated. Both the axonal type and the demyelinating type of peripheral neuropathy associated with Chédiak-Higashi syndrome have been reported.

CHS can be diagnosed in a fetus (prenatally) by examining a sample of hair from a fetal scalp biopsy or testing white blood cells (leukocytes) from a fetal blood sample. Bone marrow smears in our case revealed giant inclusion bodies in leukocyte precursor cells which were peroxidase positive. Similar observations have been made by Premalata *et al*[13]. Allogenic bone marrow transplantation(BMT) from HLA matched donor is the therapy of choice[14]. It alleviates the immune problems and the accelerated phase but does not inhibit the development of neurological disorders which become worse with age. Without BMT, children die before 10 years of age from infection or less commonly due to hemorrhage. Longer survival is possible but the lymph nodes, liver, spleen becomes enlarged and a malignant lymphoma develops. Few patients have survived 20 years of age. Infections are treated with antibiotics and abscesses are surgically drained when appropriate. Antiviral drugs such as acyclovir have been tried during the terminal phase of the disease. Cyclophosphamide and prednisone have been tried. Vitamin C therapy and granulocyte colony stimulating factor therapy has improved immune function and clotting in some patients[15]. Prognosis for Chediak-Higashi Syndrome is poor unless successfully treated with bone marrow transplant.

Allogenic bone marrow transplantation from HLA matched donor was undertaken after hospitalization in our patient along with cyclophosphamide, prednisolone and granulocyte colony stimulating factor(G-CSF) therapy. After 6 months of follow up, our patient is doing well without

any sign and symptoms of infection.

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Printed and Published by Amar Pandeya, on behalf of Late Onkar Nath Pandeya, the owner and Printed at Madona Process Studio, 3/2A, S. L. Pyne Lane, Kolkata - 700 012 and Published from Block F, 105C, New Alipore, Kolkata - 700 053.
Editor : Late Onkar Nath Pandeya.