Sohag University Sohag Medical Journal Faculty of Medicine

A rare case of Chediac Higashi Syndrome first presented by HLH and aggravated by SLE activity and viral infections.

Marwa Zanaty Elsayed[1], Omar ElHenawy[2]

1. Department of Internal Medicine, Faculty of Medicine, Sohag University, Egypt
2. Department of Clinical Pathology, Faculty of Medicine, Aswan University, Egypt

Abstract

Rare autosomal-recessive disorder Chediak-Higashi syndrome (CHS) is characterized by cutaneous hypopigmentation which also affects hair and iris, recurrent bacterial infections, deterioration of intellectual functions and an increased risk of developing hemophagocytic lympho histiocytosis (HLH), which is characterized by pancytopenia, fever, and infiltration of the liver, spleen, and lymph node by lymphocytes and histiocytes with a dismal prognosis, HLH is an accelerated phase of CHS which requires challenging treatment, our case 13 years old female patient was diagnosed with Chediak-Higashi Syndrome, who had advanced HLH aggravated by viral infection HAV(hepatitis A virus), cytomegalovirus (CMV) infection, and autoimmune disease (systemic lupus erythematosus) (SLE), she developed neurological manifestations in the form of peripheral neuropathy large azurophilic granules in granulocytes were identified by Giemsa staining and silvery hair, abnormal hypopigmented dots scattered on her body more in the upper and lower limbs which is very important for the diagnosis of this syndrome. CHS should be differentiated from other causes of partial albinism such as Griscelli syndrome.

Keywords: Chediach Higashi syndrome, CMV, HAV.
DOI : 10.21608/SMJ.2023.193138.1372

Introduction

Less than 500 cases of the very rare autosomal-recessive disease Chediak-Higashi Syndrome have been documented globally in the previous 20 years. It occurs due to a mutation in the gene for the vesicle trafficking regulatory protein family member, CHS1/LYST, which controls lysosomal trafficking . (1)

Grey hair, frequent bacterial infections, worsening neurologic issues, and coagulation issues are characteristics. Pancytopenia, hemo-phagocytosis, and significant lymphocyte infiltration of organs are all symptoms of the accelerated phase, which affects about 85% of patients progress to an accelerated phase characterized by pancytop-enia, hemophagocytosis, and significant lymphocyte infiltration of organs, leading to multi-organ failure .(2)

Thirteen years old female patient, a student, from Aswan, has another normal twin sister, and 2 normal brothers, she has primary amenorrhea.

She was delivered to a set of genetically related parents without any complications. She had a normal birth and began having problems learning at the age of seven. At the age of twelve,

she began complaining of progressive abdominal distension, along with daily and continuous fever that improved only slightly with antipyretics, arthralgia, photophobia, general malaise, and loss of appetite that lasted for about a month, recurrent attack of inferquent vomiting of a small amount of food associated with epigastric pain, change in color of the sclera, urine, and oral ulceration.

She had no bleeding history, there was a history of subjective weight loss.

The patient is not known to be diabetic or hypertensive or have any other chronic illness. At first, she received symptomatic treatment in the form of antipyretics, antiemetics, oral steroids in the form of syrup with little improvement of fever, investigations which include CBC, HAV, serum creatinine, liver function tests, abdominal U/S, CT – chest, abdomen, and pelvis were done, a few days later the condition became progressive she was deteriorated more, with continuous high-grade fever associated with tachypnea, sweating, hypotension, dry cough at first then become productive, marked general malaise and easy fatigability.

She was admitted to the oncology center as there was a strong suspicion to have lymphoma after the result of the CT scan, she received treatment in the form of vasopressor, steroids, and I.V antibiotics, fever partially improved, lymph node biopsy, bone marrow aspiration, blood sample for CMV, EBV and follow up CBC were done, one week later after discharge, she noticed painful swelling lemon size about 2*2 cm which appear after I.M injection and it was diagnosed as an abscess improved on antibiotics. Also, the patient complained of hotness and tingling sensation in the fingers, and toes of both hands, and foot, respectively.

No history of a similar condition or blood transfusion.

There is a family history of graves' disease (her uncle) and no family history of similar conditions or malignancy.

By examination, the patient had marked pallor, silvery grey hair figure [3], hypopigmented skin, figure [1]. in the form of white dots scattered all over the body more in both hands, cheeks, and legs, jaundice, hypopigmentation around the mouth, and oral ulceration.

Enlarged cervical and axillary multiple variable-sized lymph nodes some of them are amalgamated tender firm in consistency range in size from 0.5 up to 1 cm in the cervical region and from 1 to 2 C.M in the axillary area.

CBC showed (TLC-2,4/mm3 - 29% neutrophilic; Hb 9.7 g/dL; platelet count- 39,000/mm3; reticulocytes 0.8), blood film (abnormal giant intracytoplasmic granules consistent with Chediac Higashi syndrome fig (2) LFT revealed (total Bilirubin- 4.2; direct-3.4; indirect-0.80; SGPT, 108; HAV positive IgM),(CMV IgG 122; IgM 0.24; EBV, negative); ANA by IF-(positive), anti-double stranded DNA positive, anti-nucleosome antibodies positive, high CRP, (TSH;7) (serum creatinine 0.6 mg/dL; urea,39); LDH (273 U/L),(T.B gold test, negative); (serum uric acid, 5.6), hypertriglyceridemia (189 mg/dL), raised ferritin (2883 ng/mL); abdominal ultrasound showed hepato-splenomegaly. X-ray showed bilateral lung infiltrates. CT neck, chest, abdomen, pelvis revealed multiple bilateral variable sized upper, lower deep cervical L.Ns, mediastinal amalgamated LNs namely preaortic, a-orto-pulmonary, subcarinal (average size17mm), bilateral hilar forming anterior-mediastinal mass, amalgamated abdominal LNs are noted namely mesenteric, celiac, porta-hepatis, pancreatic, gastric, aortocaval, left paraaortic (16mm) forming soft tissue density mass encasing the mesenteric vessels, moderate enlarged spleen (17cm) and liver(16.5cm), cervical L.N biopsy

(Tru cut biopsy) revealed atypical lymphoid infiltrate, immunophenotyping showed(CD 20, highlighting few B cells in aggregates); (CD3, highlighting many T-cells in interfollicular areas), (CD30, small lymphoblasts, no large cells); (CD15, scattered granulocytes, no large cells) compatible with reactive LN, B.M aspiration and biopsy showed dysplasia in myeloid series in the form of hypo granulation (Chediac-Higashi granules), erythroid series showed dysplasia may be secondary to severe viral infections, autoimmune disease for clinical correlateons.

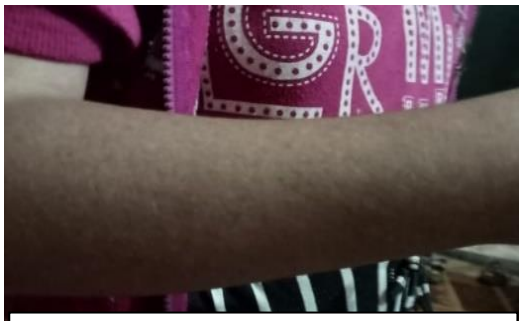

Figure (1): -Shows hypopigmentation in the arm.

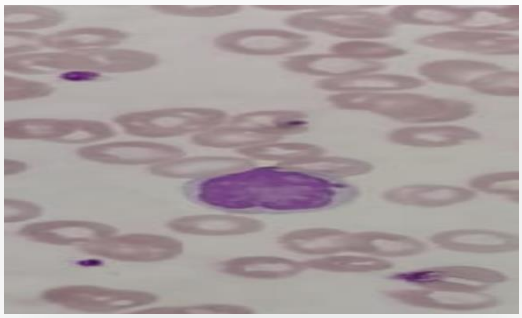

Figure (2): - Peripheral blood film showing abnormal giant intracytoplasmic granules in WBC with abnormal forms consistent with CHS, complicated by HLH.

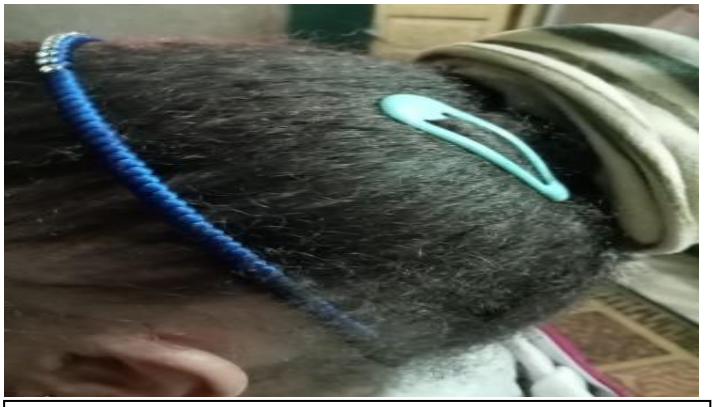

Figure (3) shows silver, grey hair.

Discussion:

Fewer than 500 cases of Chediac Higashi syndrome (CHS), an extremely rare autosomal-recessive disorder, have been documented from around the globe. Six years is the median age of start, and most victims don't make it to their tenth birthday. Abnormal vesicle fusing and a lack of lysosome transfer to the proper site of action are the results of mutations in the CHS1/LYST gene, which is located at the 1q42.1-2 locus. Hypome-lanosis, grey hair, neurological anomalies, coagulation defects, and severe immunodeficiency predict a high chance of getting HLH and are all symptoms of this condition.[2]

The hypopigmentation of skin and hair is caused by the entrapment of developed melanosomes in melanocytes. [3, 4]

Large azurophilic granules found on neutrophils improperly release their c-

ontents during bacterial or viral infections, impairing NK cell and T cell cytotoxicity and bactericidal activity. As a result, patients frequently develop recurrent skin infections and respireatory infections brought on by beta-hemolytic streptococci and Staphylococcus aureus. [5]

The combination of symptoms, including silvery grey hairs, hepatosp-lenomegaly, neurological symptoms, and coagulation defect, suggested that CHS, Griscelli syndrome, might be the cause. Hair shafts in Griscelli Syndrome have large, uneven melanin granules that are primarily found close to the medullar zone, in contrast to the uniformly distributed, regular-diameter melanin granules that are characteristic of CHS.[6]

All granule-containing cells, including melanocytes, peripheral and central nerve tissue, bone marrow cells, and peripheral blood cells, are seen to have classic giant azurophilic granules in CHS but not in Griscelli syndrome .[7]

Dysfunction of NK and cytotoxic T cells, particularly in the presence of viral infections, predisposes the emergence of HLH. Herpes group viruses have been identified as the presumed etiologic agents in the majority of virus-associated cases .[8]

The HLH-2004 group created guidelines for the identification and treatment of HLH cases with a molecular diagnosis that is concurrent with HLH do not always need to meet the diagnostic criteria; however, Only if five of the eight requirements are fulfilled are they considered met. Hemophagocytosis in the bone marrow, spleen, or lymph nodes; low or nonexistent NK-cell activity; elevated amounts of SIL-2r; fever; splenomegaly; hypertriglyceridemia; and/or hypofibrinogenemia; cytopenias impacting at least two of three lineages in peripheral blood.[9]

The HLH-2004 group's recommended treatment regimen is intended for HLH patients with or without familial or genetic disease evidence, regardless of suspected or confirmed viral infections. Patients who have both an EBV infection and a clinical picture of HLH benefit significantly from following this protocol, as shown by Horne et al.[10]

Etoposide, dexamethasone, and cyclosporine A are the main components of combination therapy. In eight weeks, 75% of people reach remission; relapses are common, though, and treatment response degrades over time. Rapid HSCT is recommended after remission has occurred. The most common cause of death in people with CHS is HLH and its complications, and once the HLH phase begins, there is little hope for recovery.[5]

References:

1. Kishore M, Marwah S, Kumar V, Suteri P, Nigam AJAoP, Medicine L. Accelerated phase of Chediak Higashi syndrome: an unusual case of pancytopenia. 2016;3(3):C156-60.

2. Kaplan J, De Domenico I, Ward DMJCoih. Chediak-higashi syndrome. 2008;15(1):22-9.

3. Lozano ML, Rivera J, Sánchez-Guiu I, Vicente VJOjord. Towards the targeted management of Chediak-Higashi syndrome. 2014;9(1):1-11.

4. Zelickson AS, Windhorst DB, White JG, Good RAJJID. The Chediak-Higashi syndrome: formation of giant melanosomes and the basis of hypopigmentation. 1967;49(6):575-81.

5. Dotta L, Parolini S, Prandini A, Tabellini G, Antolini M, Kingsmore SF, et al. Clinical, laboratory and molecular signs of immunodeficiency in patients with partial oculo-cutaneous albinism. 2013;8(1):1-10.

6. Valente N, Machado MCM, Boggio P, Alves ACF, Bergonse FN, Casella E, et al. Polarized light microscopy of hair

shafts aids in the differential diagnosis of Chédiak-Higashi and Griscelli-Prunieras syndromes. 2006;61:327-32.

7. Carlos JLA, Oliveira MV, Souza CLJJBdPeML. Chediak-Higashi syndrome: case report in afro-descendant individual. 2014;50:205-9.

8. Gopaal N, Sharma JN, Agrawal V, Lora SS, Jadoun LSJC. Chediak-Higashi Syndrome With Epstein-Barr Virus Triggered Hemophagocytic Lymphohistiocytosis: A Case Report. 2020;12.(١١)

9. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. 2007;48(2):124-31.

10. Horne A, Janka G, Maarten Egeler R, Gadner H, Imashuku S, Ladisch S, et al. Haematopoietic stem cell transplantation in haemophagocytic lymphohistiocytosis. 2005;129(5):622-30.