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Case Report

A Chronicle of Survival: A Case Study of Chediak Higashi Syndrome with Good Outcome in Pakistan

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ABSTRACT

Chediak Higashi syndrome is a unique hereditary disorder characterized by oculocutaneous albinism, mild coagulation defects, progressive neurological deficit, and an immense risk of developing hemophagocytic lymphohistiocytosis (HLH). On that account, we report a case of a three-year-old child with Chediak Higashi syndome in Rawalpindi, Pakistan. The diagnosis was established based on the congregation of classical symptoms: ocular and cutaneous hypopigmentation, repetitive infections, bleeding diathesis, and the pathognomic presence of giant granules in white blood cells.

Though the prognosis of this disease is poor in the accelerated phase with a high mortality rate, our patient upon timely diagnosis and Hematopoietic stem cell transplantation is living a healthy life now at the age of four years.

Keywords: Chediak higashi syndrome; Hypopigmentation; Bleeding diathesis; Hemophagocytic

Introduction

Chediak Higashi syndrome is a rare autosomal recessive disorder with fewer than 500 cases reported throughout the world over the last two decades[1]. In our literature review, only 15 cases have been reported in Pakistan to date among whom 7 died during their first hospital admission. It is caused by a defect in the lysosomal trafficking regulator gene LYST/CHS1, leading to abnormal protein and vesicle formation in all granule-containing cells of the body[2]. The syndrome is characterized by a triad of oculocutaneous albinism, increased susceptibility to infections, and coagulation defects[3]. A vast majority of patients with Chediak Higashi syndrome develop an accelerated phase, named hemophagocytic lymphohistiocytosis manifesting in the form of high-grade fever, hepatosplenomegaly, pancytopenia and lymphohistiocytic infiltration of spleen, liver and lymph nodes[4]. The presence of giant cytoplasmic granules in white blood cells along with regularly distributed clumped melanin along the entire hair shaft on hair microscopy strongly proposes Chediak Higashi syndrome. Detection of a pathogenic variant in the LYST/CHS1 gene acts as a confirmatory marker for Chediak Higashi syndrome[5]. Allogeneic hematopoietic stem cell transplantation (HSCT) is the treatment of choice. Based upon the scarcity of this disease, the discrete clinical and hematological picture, and a meager survival rate, we report a case of Chediak Higashi syndrome that was treated successfully via hematopoietic stem cell transplantation.

Case Presentation

The patient was a 3-year-old female who presented with abdominal pain and distention for 2 months along with 8-month history of recurring fever, occasional epistaxis, and progressive pallor.

There was a prior history of recurrent respiratory infections 5 times since birth settled for the time being with antibiotics. She is the second child from a consanguineous marriage with no family history of the disease.

Upon examination, the patient was febrile, had golden grey hair and hypopigmented skin (**Table 1**). The patient had a distended abdomen with moderate hepatosplenomegaly (**Figure 1**).

Figure 1: Photograph of our patient showing golden grey hair and hypopigmented Skin.

Table 1: Laboratory Investgations of our patient.

PARAMETERS	RESULTS	REFERENCE VALUES
Haemoglobin	7.6g/dL	4-11g/dL
Platelets	20 × 10^9/L	150-400 × 10^9/L
ESR	19mm/hr	<15mm/hr
Serum Triglycerides	3.33mmol/L	1.7mmol/L
Serum Fibrinogen	80mg/dL	200-400mg/dL
Serum Ferritin	579ng/mL	7-140ng/mL

Serum LDH, B12, folate levels, liver and renal function tests were all normal. Blood and urine cultures along with Epstein bar virus and Cytomegalovirus serology were also negative. Abdominal ultrasound confirmed hepatosplenomegaly. Peripheral blood smear confirmed Bicytopenia with giant Azurophilic Granules in neutrophils and lymphocytes (**Figure 2A,2B,2C**).

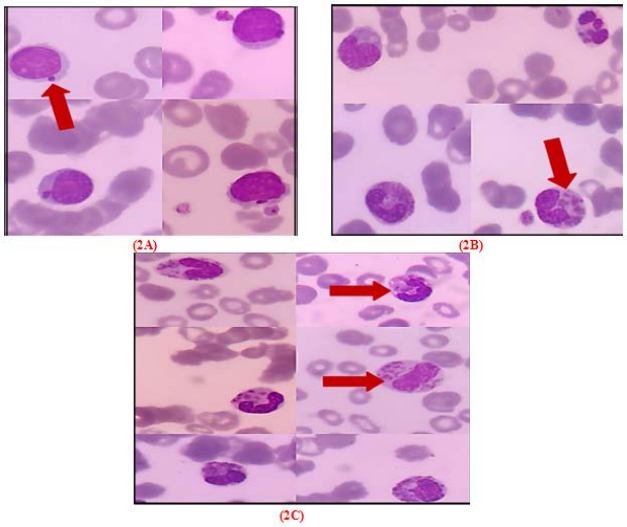

Figure 2: The Giant Azurophilic Granules in white blood cells (Red arrows)

Bone marrow examination showed hypercellular fragments and giant cytoplasmic granules in all myeloid lineage. (**Figure 3**).

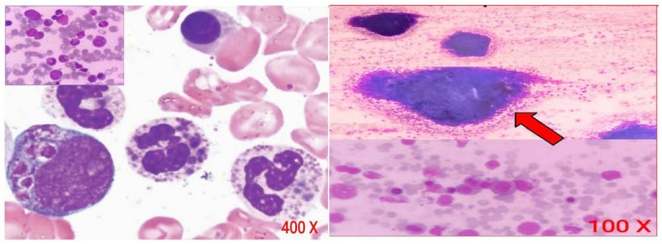

Figure 3: Hypercellular fragments with cytoplasmic granules in all myeloid lineage.

Microscopic examination of the hair shaft demonstrated the classical pattern of disease in the form of regularly distributed deposits of clumped melanin granules. (**Figure 4**).

Figure 4: A light microscope examination of hair shows abnormal clumps of melanin.

Furthermore, luckily the diagnosis was supported further by Homozygous mutation in Lyst Gene upon molecular analysis (**Table 2**).

Table 2: Diagnostic Criteria for Hlh (Accelerated phase of Chediak Higashi syndrome)

CRITERIA FOR ACCELERATED PHASE (HLH)	PATIENT FINDINGS
1. Fever	Fever (101F)
2. Splenomegaly	Splenomegaly
3. Bi / Pancytopenia in the peripheral film Hb<9.0g/dL Platelets<100× 10^9/L Neutrophils<1×10^9/L	 Hb: 7.6 g/dL Platelets: 20×10^9/L
4. Hypertriglyceridemia > 3mmol/L Hypofibrinogenemia <1.5g/L	Triglycerides : 3.33mmol/L Fibrinogen: 0.8g/L
5. Ferritin > 500ng/mL	Ferritin : 579ng/mL
6. Hemophagocytosis	
7. Loss of NK Cell activity	Absent NK Cell activity (recurrent infection)
8. sIL-2R>2400U/mL	

Therefore,the patient was started on broad-spectrum antibiotics along with dexamethasone and cyclosporine. Later on, patient was refered to the bone marrow center where a successful hematopoeitic stem cell transplant was done upon remission of the accelerated phase.

After 6 months of transplant, the girl is being followed up by a multidisciplinary team and is doing well so far.

Immunological and hematological defects have resolved with absence of any neurological manifestation.

Discussion

Beguez-Cesar was the first physician to describe Chediak Higashi syndrome in 1943, followed by Chediak and Higashi who described the maldistribution of myeloperoxidases in the neutrophilic granules of affected patients[6].

The mean age of onset is 6 years; however, most patients die before the age of 10[7].

The LYST or CHS 1 gene located on the long arm of chromosome 1(lq42-43) is associated with the development of Chediak Higashi syndrome. This gene is involved in the lysosomal trafficking transport of cytoplasmic granules. The 40 mutations consisting of nonsense, missense with deletion, and insertion[4] disrupt protein synthesis, secretory functions, and storage of lymphocytic granules (**Figure 5**)[8].

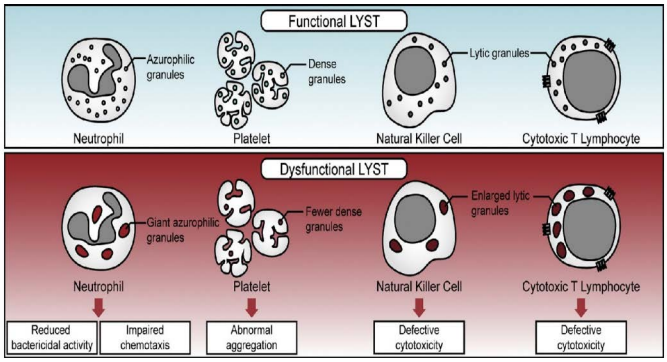

Figure 5: An image showing pathophysiology of Chediak Higashi Syndome[9].

Figure obtained from: Sharma P, Nicoli ER, Serra-Vinardell J, Morimoto M, Toro C, Malicdan MC, Introne WJ. Chediak-Higashi syndrome: a review of the past, present, and future. Drug Discovery Today: Disease Models. 2020 Jun 1;31:31-6.

Clinically this syndrome is identified by silvery grey hair, hypopigmented skin, bleeding diathesis, and recurrent respiratory and gastrointestinal infections[10], most commonly due to Staphylococcus aureus and beta-hemolytic Streptococcus[11].

The majority of the patients likewise go through an "accelerated phase," characterized by lymphohistiocytic infiltration of multiple organs precipitated particularly by Epstein-Barr virus (EBV) resulting in the development of anemia, bleeding tendency, hepatosplenomegaly, and life-threatening infections.

The presence of peroxidase-positive cytoplasmic granules mainly in neutrophils is the hallmark of Chediak Higashi syndrome[3]. Other differentials include the Griscelli syndrome, Hermansky pudlak syndrome, and Elejalde syndrome.

The patients presenting in the accelerated phase must be brought into remission by using combination therapy consisting of dexamethasone, cyclosporine, and etoposide (according to HLH 2004 protocol), before performing the definitive treatment of hematopoietic stem cell transplantation[2]. Though this treatment cures the hematologic and immunologic defects, but this therapy does not prevent the progressive neurological deficit frequently observed during long-term follow-up[5].

Conclusion

Chediak Higashi syndrome is a unique disease with a diverse spectrum of clinical presentation and investigations. The pattern that we saw throughout the literature on this syndrome is a high mortality rate due to late diagnosis of this condition. So, we wanted to add on a survival story of a now four-year-old child from a developing country living a healthy, happy life due to prompt diagnosis and management. We hope this case of ours serves as a ray of hope for all those out there who have Chediak Higashi Syndrome.

Patient Consent

Consent was taken from the father of the patient for this case report.

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