OPEN ACCESS

CASE REPORT

Chediak Higashi Syndrome with Hemophagocytic Lymphohistiocytosis

Nimra Mazhar, Aiman Mahmood Minhas, Asma Nasir, Rabia Insari, Ayisha Imran and N.A. Malik
Haematology Section, Chughtai Laboratory, Lahore.

ABSTRACT
Chediak higashi syndrome (CHS) is a rare autosomal recessive disorder caused by a genetic mutation in LYST gene. This syndrome is characterized by albinism, recurrent chest infections and neurological dysfunction. Although a rare disorder but is commonly encountered. Diagnosis of Chediak Higashi Syndrome is challenging as a result patient's remain undiagnosed leading to poor quality of life and hence they present with complications. In this case report, we discuss a 3-years-old child presented to Chughtai institute of Pathology, Lahore with fair skin greyish hair and splenomegaly. He was transfusion dependent. His bone marrow biopsy was performed showing hemophagocytic lymphohistiocytosis consistent with Chediak Higashi Syndrome with.
Key words: Chediak Higashi Syndrome, Hemophagocytic lymphohistiocytosis, LYST gene.

Introduction

Chediak higashi syndrome (CHS) is a rare autosomal recessive disorder (1, 2). Mutation in the LYST gene has been implicated to cause the disease (2, 4). It is characterized by oculocutaneous albinism, recurrent respiratory tract infections, bleeding tendency, photosensitivity and progressive neurologic dysfunction (1, 3, 4). Accelerated phase can develop in 85% of the patients with CHS.

Here, we report a case of a 3-year-old boy who presented with an accelerated phase of the disease. Diagnosis was made based on the clinical features, identification of giant granules in granulocytes present in peripheral blood and bone marrow.

CORRESPONDENCE AUTHOR
Aiman Mahmood Minhas
Haematology section,
Chughtai lab, 7- Jail road, Lahore
Email: aminhas67@gmail.com

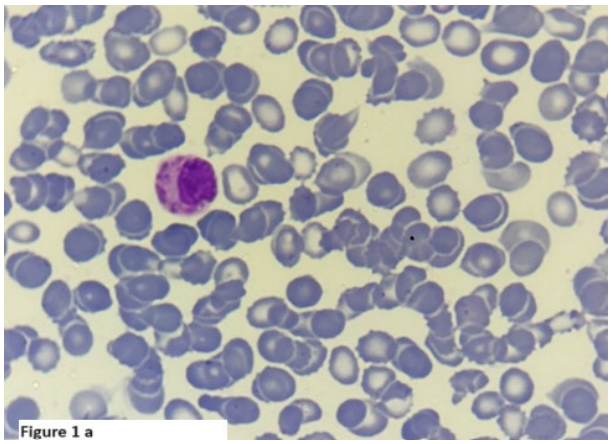
Case Presentation

A 3 years old male child presented with a history of on and off fever and lethargy for the last one year. His parents complained that the patient has been unwell for the last one year and they have observed gradual abdominal protrusion in the patient. Patient has received 6 red cell concentrates transfusions. First transfusion was done at the age of 2 years and the last was done 7 days back.

Patient's elder siblings are normal and parents have non consanguineous marriage. Family history is not significant. On examination the patient has fair skin, colored eyes (blue) and whitish gray hair. His spleen was palpable 3 fingers below left costal margin. Lymph nodes were not palpable.

Patient's bone marrow biopsy was performed under aseptic conditions after taking informed consent from his parents. His complete CBC counts were run on Sysmex NX9000 that showed Hb 15.6g/dl, total leucocyte count $2.9x10^9/L$ and platelet

4x10^9/L. His MCV was 71fL, MCH 24pg and MCHC 34g/dL. Peripheral smear showed leucopenia with occasional immature granulocytes. Neutrophils and myeloid precursors showed dense giant cytoplasmic granules. Red blood cells showed hypochromic microcytic cells with anisopoikilocytosis. Platelets were reduced on the smears with no platelet clumps.



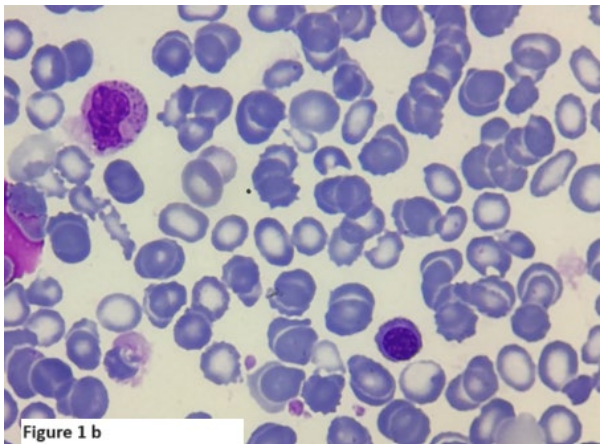
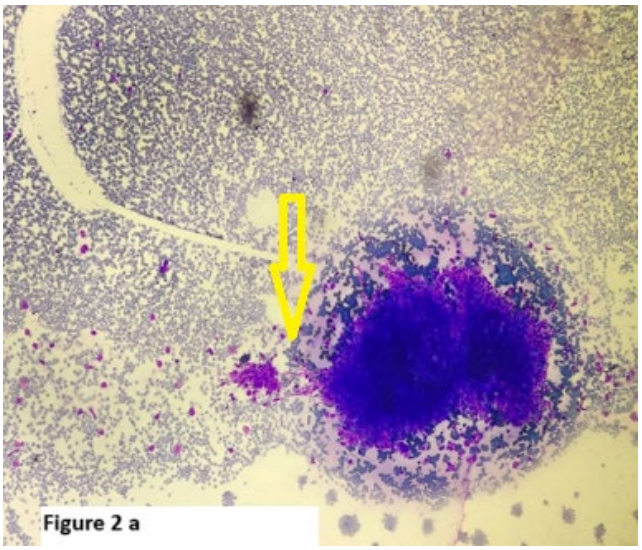


Figure 1a and 1b. Peripheral smear showing dense giant cytoplasmic granules in myelocyte

The bone marrow aspirate slides were stained using Giemsa stain. The bone marrow aspirate was hemodiluted. However, a substantial number of marrow cells were seen which constituted myeloid and erythroid precursors. Myeloid cells showed giant dense azurophilic granules. Macrophages showing hemophagocytic activity were also seen.



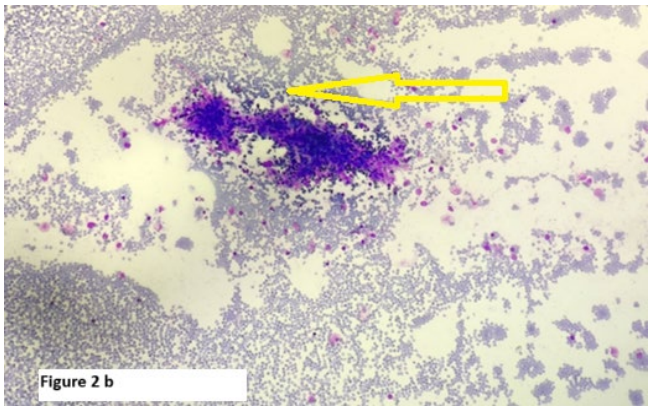


Figure 2 a and b. Bone marrow aspirate smears with hemodilution. However an increased hemophagocytic activity can be appreciated. (arrow)

Leica Pylorus tissue processor was used to prepare the trephine and H&E staining was done. Examination of the trephine biopsy revealed adequate length trephine biopsy with normal bony trabeculae and hyper cellular bone marrow (cellularity was almost 100%). Erythropoiesis was suppressed. Myelopoiesis was prominent and megakaryocytes were seen. There was marked increase in histiocytic activity. No area of infiltration was seen.

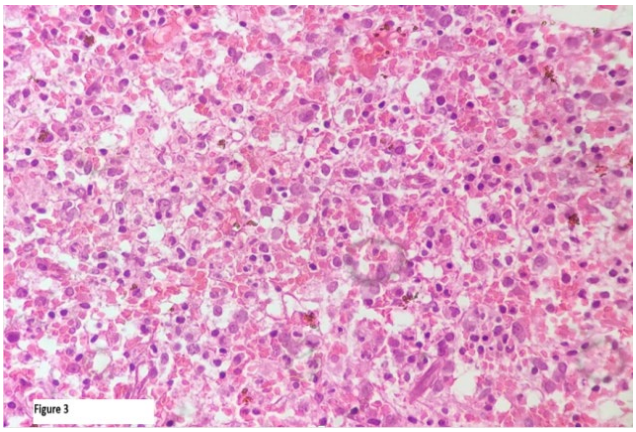


Figure 3. Bone marrow trephine biopsy section showing an increase in hemophagocytic activity.

On histochemical markers CD68 was positive in histiocytes. CD3, CD4 and CD8 were positive in T lymphocytes. CD1a was negative.

In view of clinical history and lab findings we concluded that the patient has Chediak higashi Syndrome with secondary hemophagocytic lymphohistiocytosis. We further recommended LYST mutational analysis for further work-up.

Discussion

Chediak higashi syndrome is a rare inherited autosomal recessive disorder (1, 2). This disease is characterized by a mutation in lysosomal trafficking regulator gene (LYST) (2, 4, 5, 6). LYST gene encodes a protein which is known as lysosomal trafficking regulator which as the name implies is responsible for regulating synthesis, transport and fusion of cytoplasmic vesicles (4). Mutations in the gene lead to an abnormality in the vesicles which results in grossly enlarged nonfunctional lysosomes, these lysosomes during cytology can be appreciated as giant azurophilic granules (3, 4). Presence of these granules in the peripheral blood and bone marrow forms a basis in the diagnosis of this disease (4).

As has already been discussed above, enlarged lysosomes due to a defect in LYST gene lead to a variety of clinical manifestations of the disease. In melanocytes, enlarged melanosomes cannot be properly transferred to epithelial cells and lead to hypopigmentation (3). Absent/ diminished platelet granules predispose patients to bleeding episodes (3). Due to presence of giant azurophilic granules in neutrophils, neutrophils can't release their contents in response to a bacterial or viral infection, chemotaxis is also affected this leads to impaired bactericidal activity and hence increased susceptibility to infections (3, 7). Enlarged lysosomes also lead to an impaired cytotoxic activity of T-cells and NK cells and hence lead to development of HLH (3).

Patients with CHS are prone to develop infections from *Staphylococcus aureus*, *Beta-Hemolytic Streptococci* and *Pneumococcal* species (6,8). Viral infections especially due to Epstein Barr Virus could be a cause of lymphomatous phase (8).

Chediak-Higashi syndrome is characterized by two phases, a stable phase and an accelerated phase. In the stable phase the patient has milder symptoms. However, in the accelerated phase patients usually have lymphohistiocytic infiltration, fever, peripheral neuropathy, hepatitis, pancytopenia, coagulopathy and hemorrhage (1). Around 85% of the patients who have this syndrome present in the accelerated phase of the disease (1, 4, 7). Accelerated phase consists of lymphoproliferative syndrome with hemophagocytosis and infiltration of visceral organs, fever, peripheral neuropathy, hepatitis, pancytopenia, coagulopathy and bleeding syndrome (6).

We compare our case to another documented case of Chediak Higashi Syndrome in which

a patient started experiencing fever, loss of appetite and progressive abdominal distension at the age of two years (8). On examination, this patient has fair skin, blonde hair, nystagmus and hepatosplenomegaly. Our patient also presented at the same age, moreover, symptoms and physical examination findings were same in both the cases. Peripheral blood and bone marrow examination of both revealed presence of giant granules in the leukocytes and their precursors. Clumped melanosome were appreciated in the hair examination of the patient (8). However, in our case we did not proceed with the hair shaft examination.

Treatment of CHS is usually symptomatic, infections are treated with the help of antibiotics (6). Ascorbic acid might improve the clinical outcome of the disease (6). Accelerated phase responds to Etoposide and systemic steroids (8). Treatment of CHS is limited to Bone marrow transplant (8). However, bone marrow transplant done prior to onset of accelerated phase is only known to be curative treatment option (6).

Conclusion

Patients who present with recurrent pyogenic infections should be investigated keenly. Since, presence of giant granules in the leukocytes in the peripheral blood offers one of the most important diagnostic clues and it should never be overlooked.

Timely diagnosis of CHS can prevent patients from progressing to the accelerated stage of the disease, early treatment and better disease outcomes.

References

1. Akbayram S, Akgun C, Basaranoglu M, et al. A Case of Chediak-Higashi Syndrome Presented with Hemophagocytic Lymphohistiocytosis. International Journal of Hematology and Oncology 2011; doi: 10.4999/uhod.09055.
2. Carneiro IM, Rodrigues A, Pinho L, de Jesus Nunes-Santos C, de Barros Dorna M, Moschione Castro APB,et al. Chediak-Higashi syndrome: Lessons from a single-centre case series. Allergol Immunopathol (Madr). 2019 Nov-Dec; 47(6):598-603. Doi: 10.1016/j.aller.2019.04.010. Epub 2019 Aug 30. PMID: 31477396.
3. Sharma P, Nicoli ER, Serra-Vinardell J, Morimoto M, Toro C, Malicdan MCV, et al. Chediak-Higashi syndrome: a review of the past, present, and future. Drug Discov Today Dis Models. 2020 summer; 31:31-36. Doi: 10.1016/j.ddmod.2019.10.008. Epub 2019 Dec 9. PMID: 33424983; PMCID: PMC7793027.
4. Maaloul I, Talmoudi J, Chabchoub I, Ayadi L, Kamoun TH, Boudawara T,et al. Chediak-Higashi syndrome presenting in accelerated phase: A case report and literature review. Hematol Oncol Stem Cell Ther. 2016 Jun; 9(2):71-5. Doi: 10.1016/j.hemonc.2015.07.002. Epub 2015 Aug 1. PMID: 26254864.
5. Bouatay A, Hizem S, Tej A, Moatamri W, Boughamoura L, Kortas M. Chediak-higashi syndrome presented as accelerated phase: case report and review of the literature. Indian J Hematol Blood Transfus. 2014 Sep; 30(Suppl 1):223-6. Doi: 10.1007/s12288-014-0336-x. Epub 2014 Jan 31. PMID: 25332584; PMCID: PMC4192156.
6. Song Y, Dong Z, Luo S, Yang J, Lu Y, Gao B,et al. Identification of a compound heterozygote in LYST gene: a case report on Chediak-Higashi syndrome. BMC Med Genet. 2020 Jan 6; 21(1):4. Doi: 10.1186/s12881-019-0922-8. PMID: 31906877; PMCID: PMC6943916.
7. Agarwalla S, Rao M, Dash K, Chediak-Higashi Syndrome with HLH - A Rare

Case Report. Journal Of Medical Science And Clinical Research. 2020; doi https://dx.doi.org/10.18535/jmscr/v8i6.92

8. Elfaituri SS, Matoug I. Chédiak-Higashi Syndrome: Case Report and Review of the Literature. Clin Case Rep Int. 2020; 4: 1204.

HISTORY	
Date received:	03-07-2024
Date sent for review:	23-07-2024
Date received reviewers comments:	19-08-2024
Date received revised manuscript:	30-08-2024
Date accepted:	26-08-2024

CONTRIBUTION OF AUTHORS	
AUTHOR	**CONTRIBUTION**
Nimra Mazhar	A,B,C
Aiman Mahmood Minhas	A,B,C
Asma Nasir	C
Rabia Insari	C
Ayisha Imran	A,B,C
N.A. Malik	A,B,C

KEY FOR CONTRIBUTION OF AUTHORS:

A. Conception/Study/Designing/Planning
B. Active Participation in Active Methodology
C. Interpretation/ Analysis and Discussion